UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	**Civil Action No. 3:16-md-2738-FLW-LHG** **MDL No. 2738**

THIS DOCUMENT RELATES TO ALL CASES

THE PLAINTIFFS' STEERING COMMITTEE'S OMNIBUS MEMORANDUM OF LAW IN RESPONSE AND OPPOSITION TO DEFENDANTS' JOHNSON & JOHNSON AND JOHNSON & JOHNSON CONSUMER INC.'S MOTION TO EXCLUDE PLAINTIFFS' GENERAL CAUSATION OPINIONS

[CORRECTED VERSION OF ECF DOC. 9888]

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Other Authorities

Orders

Rules

The Plaintiffs' Steering Committee ("PSC") submits this Memorandum of Law in response and opposition to *Defendants' Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Motion to Exclude Plaintiffs' General Causation Opinions* (ECF Doc. 9736). For the foregoing reasons, this Court should deny Defendants' Johnson & Johnson and Johnson & Johnson Consumer Inc.'s ("hereinafter "J&J") motion.

I. INTRODUCTION

If the PSC has produced evidence from qualified experts who have applied a reliable methodology to answer "yes" to the question of whether Johnson's *Baby Powder* and *Shower-to-Shower* (collectively "Talcum Powder Products") are capable of causing ovarian cancer, then J&J's motions must be denied, and this case must proceed to the next phase. To be clear, the question at this time is not whether the PSC's experts are right in their conclusions but rather whether the PSC's experts are qualified to offer their opinions and whether they applied reliable methodologies in reaching their opinions so that they are admissible at trial.

With respect to qualifications, there is no question that the PSC's general causation experts are nationally and internationally recognized experts in the fields of cancer epidemiology, gynecologic oncology, gynecologic pathology,

pharmacology, toxicology, and cancer biology.[1] With respect to methodology, each expert followed a rigorous and accepted methodology in assessing and weighing the scientific evidence on causation in the same manner that they and their peers use in their professional work outside of litigation. These methods include employing the causation framework and considerations described by Sir Bradford Hill in his seminal 1965 address[2] and the principles of evidence-based medicine. ("Hill Principles").

As set forth below in *Section III(A)*, there are multiple robust lines of scientific evidence relevant to the causation question at issue here. This evidence includes both published, peer-reviewed epidemiological and non-epidemiologic studies. Notwithstanding J&J's protestations as further described below, the epidemiologic evidence is largely undisputed:

- There are 35 observational studies of talcum powder and ovarian cancer of different study designs: 30 case-control studies (7 hospital based, and 24 population based), 1 pooled case-control studies, and 3 cohort studies;

[1] The PSC is concurrently filing a separate Memorandum of Law addressing the qualifications of their experts in opposition to Defendants' *Memorandum of Law in Support of Conditional Motion to Exclude Certain Plaintiffs' Experts Opinions for Lack of Qualifications* (ECF Doc. 9736-6).

[2] Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295 (1965), attached as **Exhibit 1**.

- The observational studies were conducted by different researchers in different countries, including populations in the United States, Canada, Asia, Australia and Europe;

- The overwhelming majority (n=34) of these observational studies, *irrespective of study design or population studied*, found a *positive* association (*i.e.*, a hazard ratio > 1), with most showing an association in the range of 1.1-1.7, representing a 10-70% increased risk of ovarian cancer with talcum powder use;

- In a majority of these published studies (n=19), the positive association was, in fact, statistically significant to a p=.05;

- Even in the published studies that did not show a statistically significant association, the vast majority, irrespective of design, had confidence intervals which overlapped 1.2-1.25, and were therefore consistent with a 20-25% increased risk of ovarian cancer;

- In addition to the individual observational studies, there are numerous published and unpublished meta-analyses of the observational studies as a whole. Every one of these meta-analyses show a consistent and statistically significant 25-45% increased risk of ovarian cancer; and,

- In talcum powder studies, including published meta-analyses of talcum powder cohort studies, a statistically significant risk was observed between talcum powder and a specific ovarian cancer subtype: epithelial ovarian cancer.

In addition to this consistent and largely undisputed epidemiologic data, the PSC has produced published biologic, mechanistic and other non-epidemiologic evidence to further support the conclusion that the observed association between talcum powder and ovarian cancer is indeed a *causal* association. This non-observational biologic evidence includes:

- Evidence from peer-reviewed and published studies that talcum powder can reach the ovaries *via* migration and/or inhalation, and

lymphatic transport evidence which the U.S. Food and Drug Administration (FDA) has called "indisputable."

- Evidence that when transport of talc to the ovary is blocked (by tubal ligation), the risk of ovarian cancer decreases among women exposed to talc. This is a type of "challenge and de-challenge" evidence supporting causation;
- Evidence from peer-reviewed and published studies that confirmed the presence of talc particles in ovarian cancer tissue;
- Evidence that talcum powder causes chronic inflammation and oxidative stress, both of which play an important role in carcinogenesis;
- Evidence that chronic inflammation plays an important role in initiation as well as in cancer promotion and progression; and,
- Evidence that Defendants' Talcum Powder Products contain and have contained known carcinogens such as asbestos, fibrous talc, nickel, chromium, cobalt, and fragrance chemicals.

As set forth below in *Section IV(A)*, J&J's "general causation" argument is simply a closing argument dressed-up like a *Daubert* motion, addressing virtually every issue in the case, but without any focus on the true purpose of a *Daubert* inquiry. In the guise of a methodological challenge, J&J asks this Court to evaluate the PSC's experts' conclusions contrary to the mandate of *Daubert* and its progeny. Of course, a "battle of the experts" does not provide an appropriate *Daubert*-related basis for excluding an expert's opinion that is based on sound scientific methodology.[3]

[3] *See S.E.C. v. Lucent Techs., Inc.*, 610 F. Supp. 2d 342, 351 (D.N.J. 2009) (quoting *Oddi v. Ford Motor Co.*, 234 F.3d 136, 146 (3d Cir. 2000)); *Dzielak v. Whirlpool*

In fact, the PSC's experts considered and weighed both the important evidence set forth above as well as the contrary evidence described in J&J's *General Causation* brief.[4] Underscoring that J&J's real dispute with the PSC's experts is with the conclusions they reach and not with the methodology they employ is the fact that J&J's motion relies heavily on the *ipsie dixit* opinions of their litigation experts and not authoritative texts. Obviously, any differences in opinions should be explored on cross-examination and not excluded as unreliable.

J&J makes seven (7) broad arguments in support of their motion that they claim are "methodologic errors": ***First***, they argue that the PSC's experts failed to apply "significance testing" and a rigid "hierarchy of evidence" to the observational

---

Corp., No. CV2120089KMJBC, 2017 WL 1034197, at *26 (D.N.J. Mar. 17, 2017); *Lansford-Coaldale Joint Water Auth. v. Tonolli Corp.*, 4 F.3d 1209, 1216 (3d Cir. 1993) ("'[I]n a battle of the experts, the factfinder 'decide[s] the victor.'") (alteration in original) (quoting *Mendes-Silva v. United States*, 980 F.2d 1482, 1487 (D.C. Cir. 1993))); *In re Biogen '755 Patent Litig.*, No. CV102734CCCJBC, 2018 WL 3586271, at *11 (D.N.J. July 26, 2018); *Lanzilotti by Lanzilotti v. Merrell Dow Pharm. Inc.*, No. CIV.A. 82-0183, 1986 WL 7832, at *3 (E.D. Pa. July 10, 1986) (the experts for both sides differed as to what interpretations should be given to various data. "The case was thus a classic battle of the experts, a battle in which the jury must decide the victor."); *In re Gabapentin Patent Litig.*, No. CIV.A. 00-2931, 2011 WL 12516763, at *10 (D.N.J. Apr. 8, 2011) (concluding that defendants' critiques of plaintiffs' experts' methodology and inconsistent conclusions presented "a battle of the experts, and both sides will be permitted to present expert testimony on these issues and to cross-examine the other side's expert witnesses.").

[4] *Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Memorandum of Law in Support of Motion to Exclude Plaintiffs' Experts' General Causation Opinions* (ECF Doc 9736) (hereinafter, "Defs.' Mem.")

studies to assess them for both "association" and "consistency of association."[5] ***Second,*** they argue that in addressing "strength of association," the PSC's experts "failed" to consider and acknowledge that the talcum powder-ovarian cancer association is a "weak" one most likely explained by bias and confounding.[6] ***Third,*** they claim that there is no statistically significant and consistent evidence of "dose response" that would support a causal inference under the Hill Principles.[7] ***Fourth,*** they allege that the PSC's causation experts have not offered a biologically proven mechanism that would explain the association.[8] ***Fifth***, they claim that there is no "specificity" as talcum powder has not been shown to correlate with a specific ovarian cancer subtype.[9] ***Sixth,*** they claim that one of the PSC's experts, Rebecca Smith-Bindman MD, employed an improper methodology when she performed a meta-analysis of available published studies to investigate whether regular users of talcum powder were at further increased risk for a subtype of high grade serous

[5] Defs.' Mem. at 9-13; 47-67.

[6] *Id*. at 31-47.

[7] *Id.* at 67-78.

[8] *Id.* at 78-82; *see also Defendants Johnson & Johnson And Johnson & Johnson Consumer Inc.'s Memorandum of Law in Support of Motion To Exclude Plaintiffs' Experts' Opinions Related To Biological Plausibility* (ECF Doc. 9736-1). The PSC's opposition to J&J's biologic plausibility memorandum is incorporated herein by reference.

[9] *Id.* at 82-84.

ovarian cancer (HGSOC), a subtype of epithelial ovarian cancer.[10] ***Seventh***, they complain that two of the PSC's experts, Jack Siemiatycki, MSc PhD and Patricia Moorman, PhD, have expressed opinions in this litigation on the talcum powder-ovarian cancer relationship that are inconsistent with their published papers.[11]

As set forth below, J&J's so-called "methodologic" challenges are either seriously methodologically flawed themselves or a complete and demonstrable mischaracterization of the record as follows:

First, as set forth below in *Section IV(C)*, J&J and its experts use a mechanical combination of "significance testing," risk ratios and categorizing the results using a rigid "Hierarchy of Evidence" based on generic study design to challenge the PSC's experts' opinions that there is an "association" and "consistency of association." This two-step methodology urged by J&J is itself flawed. Indeed, that unscientific two-step methodology is the basis for the PSC's motion to exclude J&J's epidemiologic experts from presenting their unreliable opinions.[12] The PSC's experts employed a proper methodology by carefully and systematically evaluating ***all*** talc-ovarian cancer studies based on sound epidemiologic principles. They

[10] *Id.* at 95-108.

[11] *Id.* at 108-120.

[12] *See* ECF No. 9737 (PSC's Motion to Exclude the Opinions of Defendants' Epidemiology Experts Karla Ballman, Ph.D., Christian Merlo, M.D., MPH, Gregory Diette, M.D., MHS, and Jonathan Borak, M.D., DABT) (hereinafter referred to as the "PSC's Motion to Exclude Defendants' Epidemiology Experts.")

carefully evaluated both statistical significance and the reported confidence intervals for each study; the individual strengths and weaknesses of each study, regardless of design, to assess the causation question; the potential biases and potential for confounding in each talc study; and they performed an assessment of (and in some cases performing) the meta-analyses of all the available studies.

Second, and as set forth below in *Section IV(D)*, J&J and their experts blatantly mischaracterize the PSC's experts' description of the "strength of association" aspect of Bradford Hill. Contrary to J&J's assertions, the PSC's experts properly resisted categorizing the strength of the talcum powder-ovarian cancer association as "weak," "moderate" or "strong" since there are no agreed upon definitions for those terms. Instead, the PSC's experts characterized the "strength of association" aspect for what it is—a 25-45% increased risk—and described it in terms of other well-accepted causal relationships like second-hand smoke and lung cancer and asbestos and lung cancer.

Third, and as set forth below in *Section IV(E*), Bradford Hill does *not* require a "statistically significant" threshold for dose response. To the contrary, because that data is so difficult to collect in most instances, Sir Bradford Hill was quite careful to describe this aspect as one that would look for *any* evidence of a dose response. In this case, and as noted by others not involved in litigation, there are multiple

observational studies which have shown evidence of a dose-response and it was proper for the PSC's experts to rely on those studies.

Fourth, and as set forth below in *Section IV(F),* the PSC's causation experts properly relied on biologic, mechanistic and other non-observational evidence to assess the "biologic plausibility" aspect of the Bradford Hill guidelines. This aspect—which J&J and its experts attempt to improperly convert from biologic "plausibility" to biologic "proof" – asks only whether it "makes sense" to call the association a causal one considering the available biologic evidence (if any). Here, there is ample biologic evidence that supports the conclusion that the association seen in the observational studies is indeed a *causal* association. This includes evidence that: 1) talcum powder and other similar particulates can migrate to the fallopian tubes and ovaries; 2) once there, talcum powder causes inflammation and oxidative stress in ovarian cells, both known mediators of cancer; and 3) the Talcum Powder Products at issue here contain known and probable carcinogens including asbestos, fibrous talc, heavy metals, and fragrance chemicals.

Fifth, and as set forth in *Section IV(G*), there is ample evidence of specificity, not only to ovarian cancer generally, but to a specific subtype of ovarian cancer—epithelial ovarian cancer.

Sixth and as set forth below in *Section IV(I),* Dr. Smith-Bindman's opinions should not be excluded. Although J&J challenges the systematic review conducted

by Dr. Smith-Bindman, she properly performed her meta-analysis. More importantly, her meta-analysis ended-up with the same estimates as essentially all of the other well-done meta-analyses and her overall conclusions about the causality of Talcum Powder Products and ovarian cancer would be exactly the same, even without her meta-analysis.

Seventh, and as set forth below in *Section IV(J)*, it was entirely proper for Drs. Siemiatycki and Moorman, both of whom had previously published in peer reviewed journals on a positive association between genital talc use and ovarian cancer, to incorporate and assess the growing body of scientific evidence demonstrating a causal association between talcum powder products and ovarian cancer. Their analyses are consistent with the growing consensus of scientific and regulatory bodies like the Institute of Medicine (2016) and Health Canada (December 2018) which recognize the probable ovarian cancer risk of talcum powder. It is also consistent with the presence of carcinogens—including asbestos—in J&J's Talcum Powder Products.

At best, J&J's challenges raise nothing more than jury-appropriate questions because at the core of their argument is the difference in the interpretation of the scientific evidence described above. Accordingly, J&J's motion must fail.

II. THE PSC'S EXPERTS AT ISSUE

The PSC has identified experts from the fields of Epidemiology, Gynecological-Oncology, Cellular Biology and Toxicology who opine that J&J's Talcum Powder Products are capable of causing ovarian cancer. While their qualifications, methodology and opinions are set forth in their expert reports, a brief summary of their background, methodology and opinions are described below:

A. THE PSC'S EPIDEMIOLOGY EXPERTS

1. Anne McTiernan, MD, PhD[13]

Dr. McTiernan is a Full Research Professor at the University of Washington School of Public Health's Department of Epidemiology and the University of Washington School of Medicine, as well as a cancer prevention researcher and a Full Member at the Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Program in Epidemiology.[14] Dr. McTiernan has spent the past 25 years in epidemiologic research, working primarily in the areas of cancer and women's health.[15] During this time, she has published over 400 manuscripts in peer-reviewed medical and scientific journals, including the Women's Health Initiative 2014 cohort

[13] Expert Report of Anne McTiernan, MD, Ph.D, Nov. 16, 2018 ("McTiernan Rep."), Exhibit A (McTiernan CV), attached as **Exhibit 2**.

[14] *See* McTiernan Rep. at 3.

[15] *Id.*

study at issue in this case.[16] Dr. McTiernan has lectured on the topic of talc and ovarian cancer, and presented testimony on this subject to the United States House of Representatives Subcommittee on Economic and Consumer Policy in 2019.[17]

Dr. McTiernan's methodology consisted of collecting and thoroughly reviewing all available published epidemiological studies, including case-control and cohort studies, systematic reviews, meta-analyses, and pooled analyses to assess whether perineal use of Talcum Powder Products can cause ovarian cancer.[18] In her review of the observational studies, she specifically examined the strengths and weaknesses of each study, evaluating the potential biases inherent in each study and the possible effects of confounding on the reported results.[19] In addition, she collected and considered biological, pathologic and mechanistic evidence, including evidence on the transport of talcum powder to the ovaries, the effect of talcum powder on cells, and the presence of carcinogens (including asbestos) in the product.[20] Having collected the observational and biologic evidence, she analyzed it according to the Bradford Hill aspects of causation and weighed the quality of

[16] *Id.* at 3-5.

[17] *See* March 12, 2019 Testimony of Anne McTiernan, House of Representatives Subcommittee on Economic and Consumer Policy ("McTiernan Congressional Statement"), attached as **Exhibit 3**.

[18] *See* McTiernan Rep. at 7.

[19] *See id*. at 22-24.

[20] *See* McTiernan Congressional Statement at 3.

evidence supporting or detracting from each piece of evidence.[21] Having done so, Dr. McTiernan expressed her conclusion that Talcum Powder Products can cause ovarian cancer and, in particular, epithelial ovarian cancer, and the magnitude of the increased risk was 22-31%.[22]

2. Jack Siemiatycki, MSc, PhD[23]

Dr. Siemiatycki is a tenured Professor of Epidemiology at the University of Montreal and Adjunct Professor of Epidemiology at McGill University. In addition to writing numerous articles on the causes and assessment of cancer-causing agents, Dr. Siemiatycki chaired the 2006 IARC Monograph panel which evaluated the carcinogenicity of Talc.[24] Prior to his retention as an expert, he was co-author of a meta-analysis on the association between talc exposure and the risk of ovarian cancer.[25] He has published more than 250 peer-reviewed articles during his career.[26]

Dr. Siemiatycki's methodology involved systematically assessing all original epidemiologic published studies, meta-analyses and opinion pieces, experimental

[21] McTiernan Rep. at 9, 68.

[22] *See* Congressional Statement at 3.

[23] Expert Report of Jack Siemiatycki, MSc, Ph.D., Nov. 16, 2018 ("Siemiatycki Rep."), Exhibit A (Siemiatycki CV), attached as **Exhibit 4**.

[24] *See* Siemiatycki Rep. at 3-4, 23-24.

[25] *See id*. at 23-24; Hilde Langseth, *et al., Perineal Use of Talc and Risk of Ovarian Cancer*, 62 J. Epidemiology Comm. Health 358 (2008), attached as **Exhibit 5**.

[26] Siemiatycki Rep. at 1.

toxicology, molecular biology, mechanistic studies, and the IARC Monograph to address the issue of general causation between perineal use of talcum powder products and ovarian cancer.[27] He exercised his expert judgment, examining each study's strengths and weaknesses and he identified potential sources of bias.[28] Dr. Siemiatycki evaluated and synthesized the totality of the data using the Bradford Hill aspects of causal inference.[29] In reaching his opinions, he objectively considered the data and scientific literature and performed his own updated meta-analysis.[30] Having done so, Dr. Siemiatycki concluded that the totality of evidence demonstrates that perineal use of talcum powder products can cause ovarian cancer and that relative risk (RR) between ever-perineal-use of Talcum Powder Products and ovarian cancer (all types combined) is 1.28 (95% CI 1.19-1.38).[31]

3. Patricia Moorman, MSPH, PhD[32]

Dr. Moorman is a tenured professor, and Director of the Clinical Research Unit at Duke University School of Medicine. Additionally, she is a member of the Duke Cancer Institute, Cancer Control and Population Sciences Program. For over

[27] *Id*. at 1-5.

[28] *See id*. at 47-61.

[29] *Id*. at 61-67.

[30] *Id*. at 33-47.

[31] *Id*. at 47.

[32] Expert Report of Patricia Moorman, MSPH, Ph.D. Nov. 16, 2018 ("Moorman Rep."), Exhibit A (Moorman CV), attached as **Exhibit 6**.

25 years, she has conducted epidemiological research on ovarian cancer, ovarian function, and women's health issues, and she has authored more than 50 publications that relate directly to ovarian cancer.[33] Her publications include a 2016 study on body powder and ovarian cancer, which reviewed the talc-ovarian cancer association, including plausible mechanisms.[34]

In this matter, Dr. Moorman's methodology, detailed in her Report, included a systemic review of all relevant literature, including original studies, pooled analyses, and meta-analyses. She additionally reviewed documents provided to her during the discovery process.[35] Dr. Moorman incorporated a weight of the evidence approach and she applied a Bradford Hill analysis, after examining the strengths and weaknesses of each study, including the internal reliability and study bias of all case-control and cohort studies.[36] Based on the accumulation of evidence linking genital talc use to ovarian cancer, Dr. Moorman concluded that Talcum Powder Products can cause ovarian cancer.[37]

---

[33] *See* Deposition of Patricia G. Moorman, MSPH, Ph.D., January 25, 2019 ("Moorman Dep.") at 41:6-8, attached as **Exhibit 7**.

[34] *See* Joellen M. Schildkraut, *et al., Association Between Body Powder Use and Ovarian Cancer: The African American Epidemiology Study (AACES)*, 25 Cancer Epidemiology Biomarkers Prev. 1411 (2016), attached as **Exhibit 8**.

[35] *See* Moorman Rep. at 9–11.

[36] *Id*. at 9–11; 38–39.

[37] *Id.* at 38.

4. Rebecca Smith-Bindman, MD[38]

Dr. Smith-Bindman is Professor in the Departments of Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Medicine, and Health Policy at the University of California San Francisco (UCSF) School of Medicine.[39] Her research expertise is in epidemiology, outcomes research, and comparative effectiveness.[40] Much of Dr. Smith-Bindman's research is in women's health, including diagnoses of cancers such as ovarian, endometrial, thyroid and breast.[41] Several of her studies have been systematic, meta-analytic, quantitative reviews of the existing published literature.[42]

Dr. Smith-Bindman's methodology to address the relationship between talcum powder products and ovarian cancer is the same as she uses in her research.[43] She reviewed 43 relevant publications, including cohort studies, systematic reviews, pooled data analyses, and case-control studies.[44] She further studied a number of

[38] Expert Report of Rebecca Smith-Bindman, MD, Nov. 16, 2018 ("Smith-Bindman Rep."), Exhibit A (Smith-Bindman CV), attached as **Exhibit 9**.

[39] *See* Smith-Bindman Rep. at 6.

[40] *Id*.

[41] *Id*.

[42] *Id*. at 6-7.

[43] *Id*. at 4.

[44] *Id*.

review articles and systematic assessments, including those completed by IARC.[45] She specifically examined the strengths and weaknesses of each study, evaluating the potential biases inherent in each.[46] She further assessed available data on migration and cellular reactions to talcum powder products and its constituents, including asbestos.[47] Dr. Smith-Bindman performed a thorough and comprehensive analysis of the Bradford-Hill causal aspects.[48] In addition, she performed a meta-analysis to explore the more specific association between regular use of talcum powder and high grade serous ovarian cancer.[49] Having done so, she concluded that the totality of evidence supports a causal association between ovarian cancer and genital exposure to Talcum Powder Products.[50]

5. Sonal Singh, MD, MPH[51]

Dr. Singh is an Associate Professor in the Department of Family Medicine and Community Health and the Meyers Primary Care Institute, with a joint appointment in the Department of Quantitative Health Sciences at the University of

[45] *Id*.

[46] *Id*. at 16-35.

[47] *Id*. at 35, 40.

[48] *Id*. at 35-41.

[49] *Id*. at 41.

[50] *Id*. at 41-42.

[51] Expert Report of Sonal Singh, MD, Ph.D, Nov. 16, 2018 ("Singh Rep."), Exhibit A (Singh CV), attached as **Exhibit 11**.

Massachusetts Medical School, Massachusetts.[52] Dr. Singh served as an advisor to the World Bank and the WHO International Agency for Research on Cancer, participating in the WHO-IARC panel, evaluating the carcinogenicity of various drugs and herbal products.[53] He has conducted several epidemiological studies, systematic reviews and meta-analysis featured in prominent medical journals, authoring more than 100 original, peer-reviewed scientific articles.[54]

Dr. Singh's methodology involved a systematic review of the epidemiologic literature and cumulative data to form his opinion concerning Talcum Powder Products' relationship to ovarian cancer.[55] He used a weight of evidence approach to evaluate all relevant data, including *in vitro*, animal, and human epidemiologic studies.[56] He analyzed the individual epidemiologic studies for both reliability and validity, noting their strengths and limitations, and specifically evaluating potential biases inherent in each study.[57] He then synthesized, examined and weighed the cumulative body of evidence using the Bradford Hill guidelines of causal

[52] *See* Singh Rep. at 3-4.

[53] *Id*. at 4.

[54] *Id*. at 5.

[55] *Id*. at 3.

[56] *Id*.

[57] *Id*. at 20-56.

inference.[58] Having done so, Dr. Singh arrived at a number of conclusions, including that there is a statistically significant increased risk of Talcum Powder Products causing ovarian cancer and that the cumulative strength of association ranges from 30% to 60%, which is similar to estimates of other established carcinogens.[59]

B. THE PSC'S GYNECOLOGIC ONCOLOGY AND PATHOLOGY EXPERTS

1. Ellen Blair Smith, MD[60]

Dr. Smith is a gynecologic oncologist certified by the American Board of Obstetrics and Gynecology. For more than 28 years, Dr. Smith treated "hundreds of women" with epithelial ovarian cancer, having been involved in all aspects of care, including diagnosis, operative care, chemotherapy selection and administration, and post-treatment care and surveillance. She also has worked with other experts at leading universities on genetic studies involving ovarian cancer patients and their daughters.[61]

Drawing on her education, training, and experience with ovarian cancer patients, Dr. Smith's methodology included a comprehensive medical literature review of epidemiological studies, mechanistic articles, and review and opinion

[58] *Id*. at 62-66.

[59] *Id*. at 16-19.

[60] Expert Report of Ellen Blair Smith, MD, Nov. 16, 2018 ("Smith Rep."), Exhibit A (Smith CV), attached as **Exhibit 11**.

[61] *See* Smith Rep. at 1.

articles. Additionally, she relied on her own educational resources and considered J&J and Imerys company documents.[62] In consideration of the talcum-powder ovarian cancer association, Dr. Smith applied a weight of the evidence approach in the context of the nine considerations of a Bradford Hill analysis.[63] In consideration of "the totality of the epidemiologic data presented in the medical and scientific literature, the biological mechanism, and the credible presence of known carcinogens in the products," Dr. Smith concluded that perineal application of "talcum powder products cause[s] the development and progression of epithelial ovarian cancer," by migration of talc through the genital tract to the fallopian tubes, ovaries and peritoneum, producing "an inflammatory… environment," which is "pro-carcinogenic." In addition to migration, talc inhalation is a "secondary route of exposure."[64]

2. Daniel Clarke-Pearson, MD[65]

Dr. Clarke-Pearson is a gynecologic oncologist certified by the American Board of Obstetrics and Gynecology. A distinguished professor at the University of North Carolina-Chapel Hill, Department of Obstetrics and Gynecology, Dr. Clarke-

[62] *Id.* at 2.

[63] *Id.* at 19–21.

[64] *Id.* at 21-22.

[65] Expert Report of Daniel Clarke-Pearson, MD, Nov. 16, 2018 ("Clarke-Pearson Rep."), Exhibit A (Clarke-Pearson CV), attached as **Exhibit 12**.

Pearson belongs to the Society of Gynecologic Oncology (SGO) and is a current member of the SGO Ethics Committee. For more than 40 years, Dr. Clarke-Pearson has been involved in the treatment, teaching, and research of gynecologic cancers, including ovarian cancer. His clinical work includes surgery, chemotherapy administration, clinical trials, and oversight of Obstetrics and Gynecology residents. He has published over 200 peer-reviewed manuscripts, written over 50 medical textbook chapters, and edited three medical textbooks.[66]

Dr. Clarke-Pearson's methodology included a systemic review of the relevant literature, including peer-reviewed papers, original research, case-controlled studies, cohort studies, meta-analysis studies, and systemic analyses. Additionally, he reviewed relevant textbooks and sought additional materials as needed. He "approached this research with the same scientific rigor" he has his "own clinical, academic, and research practice."[67] Grounded in 40 years of knowledge and experience as a gynecologic oncologist, he assessed the data "objectively and critically," considering study strengths and weaknesses by assessing "design, power, reputation of author(s), quality of journal, and potential biases," among other factors.[68] Incorporating a weight of the evidence approach, he assessed the data and

[66] *See* Clarke-Pearson Rep. at 1.

[67] *Id.* at 2.

[68] *Id.* at 2–3.

information according to its strength, applying a Bradford Hill analysis.[69] Dr. Clarke-Pearson concluded that "the use of talcum powder products, including *Johnson's Baby Powder* and *Shower-to-Shower*, applied to the perineum of women, is a causative factor in the development of EOC [epithelial ovarian cancer]," and the responsible biological mechanism is migration of talc particles to the fallopian tubes and ovaries, inciting "an inflammatory process that includes oxidative stress and specific genetic mutations."[70]

3. Judith Wolf, MD[71]

Dr. Wolf is a gynecologic oncologist certified by the American Board of Obstetrics and Gynecology. For more than 20 years, she was a professor in the Department of Gynecologic Oncology at University of Texas—San Antonio. Dr. Wolf's area of expertise is ovarian cancer - "diagnosis, research, treatment, and patient advocacy."[72] She has authored or co-authored over 100 peer-reviewed research articles and was the principal investigator or co-investigator for eleven research grants related to gynecologic cancers. She also has served as an investigator or collaborator on 84 protocols, spoken at over 50 conferences, and presented at

[69] *Id.* at 3, 8–9.

[70] *Id.* at 9–10.

[71] Expert Report of Judith Wolf, MD, Ph.D, Nov. 16, 2018 ("Wolf Rep."), Exhibit A (Wolf CV), attached as **Exhibit 13**.

[72] *Id.* at 1.

"numerous" scientific exhibitions and seminars. "The majority of these have dealt with some aspect of ovarian cancer."[73]

Dr. Wolf's methodology was "similar" to the method and "rigor" she has used routinely in her professional practice, stemming 30 years.[74] Dr. Wolf reviewed "an extensive body" of medical and scientific literature, including epidemiologic, animal, and mechanistic studies. She considered selection and recall bias, and assessed internal reliability and validity, for study strengths and weaknesses.[75] She additionally reviewed pertinent textbooks as well as documents and testimony exchanged in this matter.[76] She used a weight of the evidence method, applying the Bradford Hill concepts,[77] only forming an opinion on causation after reviewing "all of the literature" "as a whole."[78] Dr. Wolf concluded that "talcum powder products cause epithelial ovarian cancer in some women," presenting "a significant risk factor for ovarian cancer for *all* women who use the products."[79] She determined that the mechanism by which talc causes ovarian cancer is migration of talc particles through

[73] *See* Wolf Rep. at 1.

[74] *Id.* at 1–3.

[75] *Id.* at 2–3; *see also id.* at 7, 24.

[76] *Id.* at 2–3.

[77] *Id.* at 2–3; 13–17.

[78] *See* Deposition of Judith K. Wolf, MD, January 7, 2019 ("Wolf Dep.") at 58:9-59:5, attached as **Exhibit 14**.

[79] Wolf Rep. at 16.

the genital tract, inducing inflammation and oxidative stress, enabling carcinogenesis.[80] Inhalation is a second mechanism.[81]

4. Sarah Kane, MD[82]

Dr. Kane is a gynecologic pathologist, certified by the American Board of Pathology in Anatomic Pathology, Clinical Pathology and Cytopathology.

Dr. Kane's methodology involved her addressing the relationship between talc and ovarian cancer in terms of plausibility and mechanism as well as based on the cumulative epidemiological evidence.[83] More particular to this litigation, Dr. Kane reviewed the epidemiologic literature in-depth regarding talcum powder and ovarian cancer from the perspective of a gynecologic pathologist.[84] She also evaluated a substantial body of biologic evidence relevant to the question of causation.[85] Her general causation opinion is based on considering the epidemiological as well as non-epidemiology lines of evidence, weighing that evidence based on a range of considerations that she described in detail in her

[80] Wolf Rep. at 16–17.

[81] *Id.*

[82] Expert Report of Sarah E. Kane, MD, Nov. 16, 2018 ("Kane Rep."), Exhibit A (Kane CV), attached as **Exhibit 15**.

[83] *See* Kane Rep. at 4-5 and 9-37.

[84] *Id*., at 6-9; 16-29.

[85] *Id*. at 4-29.

report,[86] and applying the Bradford Hill causation guidelines.[87] In addition to the epidemiologic evidence in case control studies, cohort studies, meta-analyses, and pooled analyses, she considered the mechanism of talc's carcinogenicity,[88] the role of inflammation,[89] the role of the immune system in carcinogenesis,[90] talc migration, translocation, inhalation and lymphatic transport,[91] the significance of talc found in tissue,[92] and evidence of dose-response in the studies that had the data to assess it. She looked at all evidence, both in favor of a causal effect and opposed to it and weighed the evidence using a "weight of evidence" methodology.[93] Dr. Kane has concluded that talcum powder products are a likely cause of ovarian cancer.[94]

---

[86] *Id.* at 3-9.

[87] *Id*. at 33-37.

[88] *Id*. at 9-10, 16–29.

[89] *Id*. at 10-13

[90] *Id*. at 13

[91] *Id*. at 14

[92] *Id*. at 14-15

[93] *Id*. at 3-9 (methodology); 10-37 (analysis of epidemiological and non-epidemiological lines of evidence).

[94] *Id*. at 4-5, 37.

C. THE PSC'S TOXICOLOGY & CELLULAR BIOLOGY EXPERTS

1. Laura Plunkett, PhD, DABT[95]

Dr. Plunkett is a pharmacologist, toxicologist and United States Food and Drug Administration (FDA) regulatory specialist who was a Professor of pharmacology and toxicology at the University of Arkansas and has written dozens of peer-reviewed articles and book chapters and presented at numerous conferences and seminars on issues related to pharmacology, toxicology, and pharmacokinetics.[96]

The methodology Dr. Plunkett employed to assess the talcum powder-ovarian cancer causal question is described in her report and deposition[97] and included "human health risk assessment," a "'weight-of-the-evidence' assessment" to systematically evaluate individual studies for the strengths and weaknesses of each study, including the study design.[98] She weighed the quality of evidence supporting

[95] Expert Report of Laura Plunkett, Ph.D, DABT, Nov. 16, 2018 ("Plunkett Rep."), Exhibit A (Plunkett CV), attached as **Exhibit 16**.

[96] *See* Plunkett Rep. at 3-6; Plunkett CV at 4-15.

[97] *See* Plunkett Rep. at 6-9; Deposition of Laura Plunkett, Ph.D., DABT, December 19, 2018 ("Plunkett Dep.") at 75:15- 93:9; 116:23-118:11, attached as **Exhibit 17**.

[98] Plunkett Rep. at 35, 40, 41, 61; Plunkett Dep. at 38:13-39:13; 79:4-25; 102:9-16; 239:3-16; and 240:23- 241: 8.

or detracting from each.[99] Dr. Plunkett concluded that the "the weight-of-the-evidence indicates that genital exposure to talcum powder products increases the risk of ovarian cancer in women. This conclusion is supported by data that includes, but is not limited to the following: (1) the known toxic effects of talc and the other components of talcum powder products; (2) studies that have identified biologically plausible mechanisms for cancer in humans; (3) the likelihood that talc particles can reach the ovaries; (4) the existence of a dose-response relationship for toxicity, including the risk of cancer; and (5) the large human database that includes studies conducted over a period of 40 years showing a consistent signal for ovarian cancer in women exposed to talcum powder products."[100] She further concluded that "When considered together, the scientific literature on the biological effects of talc, as well as asbestos and other constituents routinely found in talc… provide sufficient evidence to show that these chemicals produce cellular changes that have been linked to carcinogenesis and that the biological mechanism for carcinogenesis (ovarian and/or lung) following exposure to talcum powder products likely involves induction of a chronic inflammatory response."[101]

---

[99] Plunkett Rep. at 8, 9, 29, 31,38, 51,52, 77; Plunkett Dep. at 37:24-38:12; 79:4-25; 102:9-16; 106:14-107:6; 134:16-135:17; 183:19-184:6; 198: 9-199:14; 204:20-205:11;217:17-218:20; 239:3-16; and 239:23-241:8.

[100] Plunkett Rep. at 77.

[101] Plunkett Rep. at 46. *See also, id.*, at 19,23,27-8, 38,40, 42-3, 48.

2. Arch Carson, PhD[102]

Dr. Carson is a physician and toxicologist who specializes in the practice of medical toxicology. He is an Associate Professor at the University of Texas School of Public Health in Houston, Texas, and the Program Director of the Occupational and Environmental Medicine Residency training program at the University of Texas Health Science Center at Houston.[103]

The methodology Dr. Carson employed to assess the talcum powder-ovarian cancer causal question is described in his report and deposition[104] and included a review of the relevant published scientific and medical literature. He systematically evaluated the individual studies for consistency, paying particular attention to the potential biases and confounding inherent in each study as considered by the investigators of the various primary studies, [105] and he also considered the different study designs.[106] In reaching his causation opinions, he undertook a Bradford Hill analysis.[107] Dr. Carson concluded the perineal use of Talcum Powder Products for

---

[102] Expert Report of Arch Carson, MD, Ph.D, Nov. 16, 2018 ("Carson Rep."), Exhibit A (Carson CV), attached as **Exhibit 18**.

[103] *See* Carson Rep. at 1.

[104] *Id.* at 1, 11. *See also* Deposition of Arch Carson, MD, Ph.D., Jan. 19, 2019 ("Carson Dep.") at 40:9-43:22; 49:10-54:23; 172:11-176:3; and 214:1-218:4, attached as **Exhibit 19**.

[105] Carson Rep. at 8-9; Carson Dep. at 210:18-211:1.

[106] Carson Dep. at 240:19-241:20.

[107] Carson Rep. at 8-11.

feminine hygiene purposes results in direct exposure to the female reproductive tract via migration of powder through the upper genital tract to the ovary and that inhalation is a secondary route of exposure.[108] He concluded that (a) "perineal use of Talcum Powder Products causes ovarian cancer in some users and increases the risk of ovarian cancer in all users of these products," and[109] (b) "the currently available scientific research, when considered in its totality, demonstrates a cause and effect relationship between the use of Talcum Powder Products and the development of epithelial ovarian cancer."[110]

III. FACTUAL AND LEGAL BACKGROUND

In order to address J&J's methodologic challenge to the PSC's experts, it is important to summarize the epidemiologic and non-epidemiologic evidence against which the current dispute arises. That evidence, which spans decades and involves dozens of studies, is summarized in *III(A)*. It is also important to understand that three (3) courts, a federal court in South Dakota, state court in Missouri, and a state court in Georgia have all *denied* similar general causation *Daubert* challenges that J&J has raised here. Those cases, which J&J ignores, and the New Jersey and California state cases which it highlights, are discussed in *Section III(C)*.

[108] *Id.* at 8-11.

[109] *Id*. at 1.

[110] Carson Rep. at 11.

A. TALCUM POWDER AND OVARIAN CANCER GENERAL CAUSATION EVIDENCE

1. Epidemiologic and Observational Data

Epidemiology is the science of occurrence of diseases in human populations. It is concerned with the patterns of disease occurrence and also with identifying the factors that influence disease occurrence.[111]

As with most other now-known carcinogens, such as asbestos and tobacco, it is both unethical and pragmatically impossible to conduct clinical trials to investigate whether a given exposure causes cancer in humans.[112] Therefore, scientific assessment as to whether talc causes ovarian cancer is based on epidemiologic studies in which the investigators collected and analyzed information on exposures (*i.e.*, talc use and other risk factors), rather than studies in which exposures were randomly assigned to the study subjects in an experimental setting. Observational study designs used in the study of talcum powder and risk of ovarian cancer include case-control studies and cohort studies. Both of these types of observational studies are well-established and generally accepted methods for studying cancer etiology.[113]

---

[111] Siemiatycki Rep. at 5.

[112] Kenneth Rothman, *et al., Modern Epidemiology* (3d ed. 2009) at 29, attached as **Exhibit 20**.

[113] *Id. See also* Moorman Rep. at 15; *Reference Manual on Scientific Evidence*, Federal Judicial Center, Third Edition (2011) at 555-6 (hereinafter "*Ref. Man.*"). The Federal Judicial Center is the research and education agency of the federal judicial

a. Talcum powder and ovarian cancer case-control studies

In case-control studies, participants are diagnosed with a specific type of cancer (cases) and are compared with otherwise similar participants who have not been diagnosed with cancer (controls). Ideally, controls will be similar to the cases on all variables other than the exposure under question. The investigators then analyze whether cases are more likely than the controls to have a given exposure. Case-control studies can enroll a large number of cases, are usually less expensive than cohort studies, and can be completed over shorter periods of time. Case-control studies focus on a single disease, therefore they typically collect more detailed risk factor information for that disease than cohort studies. A major advantage of case-control studies is that they are a more efficient design for studying diseases that are less common or have a long latency period. Therefore, they are very commonly used for etiologic studies of cancer. A disadvantage of case-control studies is that they collect exposure information for the cases after they have already been diagnosed

system. It was established by Congress in 1967 (28 U.S.C. §§ 620-629 (2015)), on the recommendation of the Judicial Conference of the United States, with the mission to "further the development and adoption of improved judicial administration in the courts of the United States." *Id.* at xiii-xvi; *see also* Federal Judicial Center, http://www.fjc.gov (last visited Nov. 15, 2018). The PSC refers to the *Reference Manual* (in addition to case law) throughout this brief because it is designed to assist judges on science issues, including *Daubert.*

with the disease, which raises concerns that cases may recall exposures differently from controls, *i.e.* recall bias.[114]

In 1982, a case-control study by Cramer, *et al.* was the first to find an increased risk for ovarian cancer associated with talc use.[115] There are 35 observational studies of talcum powder and ovarian cancer that have been conducted overall: 30 case-control studies (7 hospital based, and 23 population based),[116] 1

---

[114] McTiernan Rep. at 8.; *Ref. Man.* at 555-5; *Modern Epidemiology* at 111-127.

[115] Daniel W. Cramer, *et al., Ovarian Cancer and Talc: A Case-Control Study*, 50 Cancer 372 (1982), attached as **Exhibit 21**.

[116] Cramer (1982); Patricia Hartge, *et al., Talc and Ovarian Cancer*, 250 JAMA 1844 (1983), attached as **Exhibit 22**; Alice S. Whittemore, *et al., Personal and Environmental Characteristics Related to Epithelial Ovarian Cancer*, 128 Am. J. Epidemiology (1988), attached as **Exhibit 23**; Bernard L. Harlow & Noel S. Weiss, *A Case –Control Study of Borderline Ovarian Tumors: the Influence of Perineal Exposure to Talc*, 130 Am. J. Epidemiology 390 (1989), attached as **Exhibit 24**; *M. Booth, Risk Factors for Ovarian Cancer: a Case-Control Study*, 60 Brit. J. Cancer 592 (1989), attached as **Exhibit 25**; Bernard L. Harlow, *et al*, *Perineal Exposure to Talc and Ovarian Cancer Risk*, 80 Obstetrics & Gynecology 19 (1992), attached as **Exhibit 26**; Patricia Hartge & Patricia Stewart, *Occupation and Ovarian Cancer: A Case-Control Study in the Washington, DC, Metropolitan Area*, 1978-1981, J. Occupational Med. 924 (1994), attached as **Exhibit 27**; Karin A. Rosenblatt, *et al., Mineral Fiber Exposure and the Development of Ovarian Cancer* 45 Gynecologic Oncology 20 (1992), attached as **Exhibit 28**; Yong Chen, *et al., Risk Factors for Epithelial Ovarian Cancer in Beijing, China*, 21 Int'l J. Epidemiology 23 (1992), attached as **Exhibit 29**; Anastasia Tzonou, *et al., Hair Dyes, Analgesics, Tranquilizers and Perineal Talc Application as Risk Factors for Ovarian Cancer*, 55 Int'l J. Cancer 408 (1993), attached as **Exhibit 30**; David Purdie, *et al., Reproductive and Other Factors and Risk of Epithelia Ovarian Cancer: an Australian Case-Control Study*, 62 Int'l J. Cancer 678 (1995), attached as **Exhibit 31**; Asher Shushan, *et al., Human Menopausal Gonadotropin and the Risk of Epithelial Ovarian Cancer*, 65 Fertility & Sterility 13 (1996), attached as **Exhibit 32**; Adele Green, *et al., Tubal Sterilization, Hysterectomy and Decreased Risk of*

Ovarian Cancer,71 Int'l J. Cancer 948 (1997), attached as **Exhibit 33**; Stella Chang & Harvey A. Risch, *Perineal Talc Exposure and Risk of Ovarian Carcinoma*, 79 Cancer 2396 (1997), attached as **Exhibit 34**; Linda S. Cook, *et al., Perineal Powder Exposure and the Risk of Ovarian Cancer*, 145 Am. J. Epidemiology 459 (1997), attached as **Exhibit 35**; Beatrice Godard, *et al., Risk Factors for Familial and Sporadic Ovarian Cancer Among French Canadians: a Case-Control Study*, 179 Am. J. Obstetrics & Gynecology 403 (1998), attached as **Exhibit 36**; Daniel W. Cramer, *et al., Genital Talc Exposure and Risk of Ovarian Cancer*, 81 Int'l J. Cancer 351 (1999), attached as **Exhibit 37**; Cheung Wong, *et al., Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: a Case-Control Study*, 93 Obstetrics & Gynecology 372 (1999), attached as **Exhibit 38**; Roberta B. Ness, *Factors Related to Inflammation of the Ovarian Epithelium and Risk of Ovarian Cancer*, 11 Epidemiology 111 (2000), attached as **Exhibit 39**; Paul K Mills, *et al., Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*, 112 Int'l J. Cancer 458 (2004), attached as **Exhibit 40**; Malcolm C. Pike, *et al., Hormonal Factors and the Risk of Invasive Ovarian Cancer: a Population-Based Case-Control Study*, 82 Fertility & Sterility 186 (2004), attached as **Exhibit 41**; Susan J. Jordan, *et al., Risk Factors for Benign Serous and Mucinous Epithelial Ovarian Tumors*, 109 Obstetrics & Gynecology 647 (2007), attached as **Exhibit 42**; Melissa A. Merritt, *et al*., Talcum Powder, Chronic Pelvic Inflammation and NSAIDs in Relation to Risk of Epithelial Ovarian Cancer, 122 Int'l J. Cancer 170 (2008), attached as **Exhibit 43**; Patricia G. Moorman, *et al., Ovarian Cancer Risk Factors in African-American and White Women,* 170 Am. J. Epidemiology 598 (2009), attached as **Exhibit 44**; Anna H. Wu, et al., *Markers of Inflammation and Risk of Ovarian Cancer in Los Angeles County*, 124 Int'l J. Cancer 1409 (2009), attached as **Exhibit 45**; Karin A. Rosenblatt, *et al.*, Genital Powder Exposure and the Risk of Epithelial Ovarian Cancer, 22 Cancer Causes Control 737 (2011), attached as **Exhibit 46**; Michelle L. Kurta, *et al., Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a U.S.-Based Case-Control Study*, 21 Cancer Epidemiology Biomarkers Prev. 1282 (2012), attached as **Exhibit 47**; Anna H. Wu, et al., *African-Americans and Hispanics Remain at Lower Risk of Ovarian Cancer than Non-Hispanic Whites After Considering Non-Genetic Risk Factors and Oophorectomy Rates*, 24 Cancer Epidemiology Biomarkers Prev. 1094 (2015), attached as **Exhibit 48**; Daniel W. Cramer, *et al., The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*, 27 Epidemiology 334 (2016), attached as **Exhibit 49**; Schildkraut (2016).

pooled study,[117] and 3 cohort studies.[118] The overwhelming majority (n=34) of these studies, irrespective of study design, found a positive association (i.e., a hazard ratio > 1), with most showing an association in the range of 1.1-1.7, representing a 10-70% increased risk of ovarian cancer with talcum powder use. In a majority of the published studies (n=19), the association reported was statistically significant.

J&J claims that these data may be unreliable based on bias and confounding. However, and as discussed in *Section IV(D)(2)*, the PSC's causation experts and many study's authors have concluded that both bias and confounding were unlikely in the talcum case-control studies. Some of the statements from the literature are:

- "In studies where the exposure is simple (e.g., never versus ever use), recall bias is unlikely to be an important source of bias. The positive association is strongest for the serous histologic type (Penninkilampi *et al.* (2018); Berge *et al.* (2018); Taher *et al.* (2018)); findings that the association may vary by histologic type

[117] Kathryn L. Terry, *et al.*, *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 85,25 Cases and 9,859 Controls*, 6 Cancer Prev. Research 811 (2013), attached as **Exhibit 50**.

[118] Presented in five published papers. Dorota M. Gertig, *et al.*, Prospective Study of Talc Use and Ovarian Cancer, 92 J. Nat'l Cancer Inst. 249 (2000), attached as **Exhibit 51**; Margaret A. Gates, *et al.*, *Talc Use, Variants of the GSTM1, GSTT1, and NAT2 Genes, and Risk of Epithelial Ovarian Cancer*, *17 Cancer Epidemiology Biomarkers Prev. 2436* (2008), attached as **Exhibit 52**; Margaret A. Gates, *et al.*, Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype, 171 Am. J. Epidemiology 45 (2010), attached as **Exhibit 53**; Serena C. Houghton, *et al.*, Perineal Powder Use and Risk of Ovarian Cancer, 106 J. Nat'l Cancer Inst. (2014), attached as **Exhibit 54**; NL Gonzalez, *et al.*, Douching, Talc Use, and Risk of Ovarian Cancer, 27 Epidemiology 797 (2016), attached as **Exhibit 55**.

detracts from the hypothesis of report bias, as the type of bias would likely operate for all histologic types."[119]

- "In addition, the exposure definition of genital talc use at least once per week may have decreased the influence of recall bias in this analysis, since habitual talc use is likely to be recalled more accurately than sporadic use."[120]

- "Methodological factors such as recall bias should always be considered in case-control studies. It could have been a problem had there been wide-spread publicity about the possible association between use of body powder and cancer. The International Agency for Research on Cancer (IARC) the working group considers that there has not been widespread public concern about this issue and therefore considers it unlikely that such a bias could explain the consistent findings."[121]

- "Recall bias has also been implicated as a limitation in studies of talc and ovarian cancer. However, findings in a prospective study, the Nurses' Health Study, in which exposure data were collected prior to diagnosis and hence free of recall bias, were similar to the present study finding for talc use and serous invasive ovarian cancer. It has also been suggested that use of talc is habitual *versus* memorable and not likely to be subject to recall bias."[122]

- "In summary, we have demonstrated a consistent association between talc and ovarian cancer that appears unlikely to be explained by recall or confounding."[123]

---

[119] Health Canada, *Draft Screening Assessment, Talc* (December 2018) ("Health Canada Assessment") at 28, attached as **Exhibit 56**.

[120] Gates (2008) at 9.

[121] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 93: *Carbon Black, Titanium Dioxide and Talc* (2010) at 409, attached as **Exhibit 57**; Langseth (2008) at 358.

[122] Mills (2004) at 464.

[123] Cramer (1999) at 356.

b. Talcum powder and ovarian cancer cohort studies

In cohort studies, the exposures of a group (cohort) of people who are assumed to be healthy are assessed, and the group is followed over a period of time. During the follow-up period, some members of the cohort will be diagnosed with cancer, while others will not, and comparisons are then made between these two groups. Cohort studies may need to be very large (up to hundreds of thousands of participants) to have sufficient statistical power to identify factors that may increase cancer risk by on the order of 20 or 30 percent. They also have to be of sufficient duration to account for the development for cancer, *i.e.*, the latency.

Importantly, cohort studies must identify exposures of interest when participants are enrolled into the study in order to determine effect of the exposures on eventual development of the outcome of interest (cancer). Alternatively, if an exposure is ascertained at some time *after* enrollment the researchers will consider the date of collection of that exposure data to be the start date for follow-up of study participants. Because cohort studies typically are designed to look at multiple outcomes such as cancers, cardiovascular diseases, mortality, and other diseases, information collected on exposures tends to be minimal, to pertain to current levels of exposure, and may not be updated during follow-up. As illustrated in the forest plot below, the results of 4 of the 5 published studies regarding the three cohorts

showed a positive association and the confidence intervals of all 5 were consistent with the 20-25% increased risk seen in the case-control studies:

Cohort	Study	RR	Lower CI	Upper CI	← Decreased Risk ←	→ Increased Risk →
Nurse's Health Study	Gertig (2000)	1.09	0.86	1.37		
	Gates (2008)*	1.24	0.83	1.83		
	Gates (2010)	1.06	0.89	1.28		
Women's Health Initiative	Houghton (2014)	1.06	0.87	1.28		
Sister Study	Gonzalez (2016)	0.73	0.44	1.2		

* Nested Case-Control Study

c. Comparison of talcum powder and ovarian cancer observational studies

Observational studies, including cohort studies and case-control studies, each have advantages and disadvantages for evaluating talc as a risk factor for ovarian cancer. No single study design is clearly superior to the other.[124] In fact, placing observational studies on a "hierarchy" or "pyramid," as J&J and its experts do, has been called a "misconception."[125] As has been observed: "the type of study should not be taken as a guide to a study's validity."[126]

[124] Kenneth J. Rothman, *Six Persistent Research Misconceptions*, 29 J. Gen. Internal Med. 1060 (2014), attached as **Exhibit 58**.

[125] *Id.*

[126] *Id.* at 1061.

The specific details related to the conduct of the study such as methods of exposure assessment, length of follow-up and choice of control group can impact the validity of the findings and the interpretation of results. As such, rather than making a conclusion based only on the overall study design, the evaluation and interpretation of the findings of the studies must consider the strengths and weaknesses of the individual studies.[127]

As set forth below, the PSC's experts considered the biases and potential confounders for all talc studies—case control and cohort. In contrast, in the summary of epidemiology contained in their brief, J&J choses to *only* describe the talcum powder cohort studies.[128] Its' decision is misleading because, as can be seen in the Forest-plot below,[129] almost all case-control studies, regardless of their study design,

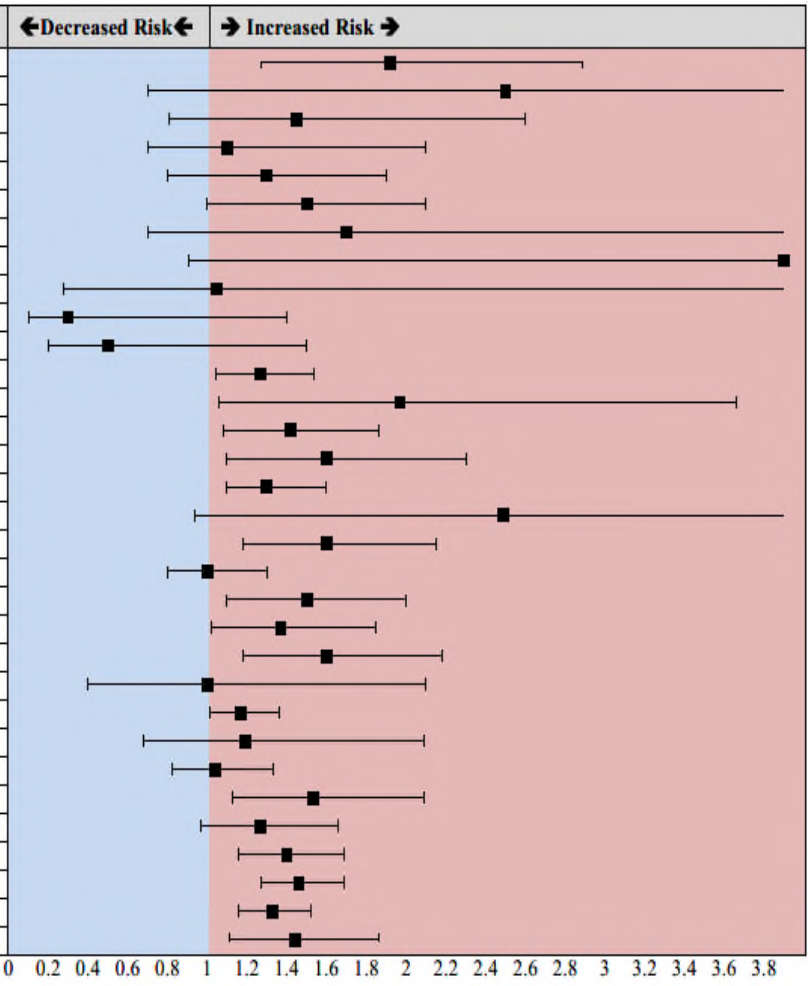
[127] *See* Moorman Rep. at 8; Deposition of Anne McTiernan, MD, Ph.D., January 28, 2019 ("McTiernan Dep.") at 116:20-118:24 (discussing that the hierarchy of the reliability of epidemiology evidence depends on the question under review), attached as **Exhibit 59**; Siemiatycki Rep. at 10 ("[V]alidity and reliability are not determined by the overall architecture of the study, but rather by the specifics of the study… There may be many reasons why a particular case-control study is more valid than a particular cohort study.").

[128] *See* Defs.' Mem. at 14-17.

[129] Siemiatycki Rep. at 95-97.

demonstrated a consistent increased risk between use of Talcum Powder Products and ovarian cancer:

Study	RR	L. CI	U. CI
Cramer 1982	1.92	1.27	2.89
Hartge 1983	2.50	0.70	10.00
Whittemore 1988	1.45	0.81	2.60
Harlow & Weiss 1989	1.10	0.70	2.10
Booth 1989	1.30	0.80	1.90
Harlow 1992	1.50	1.00	2.10
Rosenblatt 1992	1.70	0.70	3.90
Chen 1992	3.90	0.91	10.60
Tzonou 1993	1.05	0.28	3.98
Hartge & Stewart 1994 (5-9 yrs.)	0.30	0.10	1.40
Hartge & Stewart 1994 (10+ yrs.)	0.50	0.20	1.50
Purdie 1995	1.27	1.04	1.54
Shushan 1996	1.97	1.06	3.66
Chang & Risch 1997	1.42	1.08	1.86
Cook 1997	1.60	1.10	2.30
Green 1997	1.30	1.10	1.60
Godard 1998	2.49	0.94	6.58
Cramer 1999	1.60	1.18	2.15
Wong 1999	1.00	0.80	1.30
Ness 2000	1.50	1.10	2.00
Mills 2004	1.37	1.02	1.85
Pike 2004	1.60	1.18	2.18
Jordan 2007	1.00	0.40	2.10
Merritt 2008	1.17	1.01	1.36
Moorman 2009 (Afr. Am.)	1.19	0.68	2.09
Moorman 2009 (Cauc.)	1.04	0.82	1.33
Wu 2009	1.53	1.13	2.09
Rosenblatt 2011	1.27	0.97	1.66
Kurta 2012	1.40	1.16	1.69
Wu 2015	1.46	1.27	1.69
Cramer 2016	1.33	1.16	1.52
Schildkraut 2016	1.44	1.11	1.86



d. Talcum powder and ovarian cancer meta-analyses

Since there can be random variations within individual epidemiologic studies, and because very large sample sizes may be needed to study rare diseases like ovarian cancer, epidemiologists seldom (if ever) make causal inferences based on results of one study. Rather, they look at the totality of epidemiologic studies to determine patterns of exposure-disease relationships. Meta-analysis is a method used

to combine the statistical results of several studies to produce an average estimate of effect of an exposure on an outcome of interest. The summary estimates can provide evidence regarding the presence or absence of an association and can allow examination of dose-response relationships.[130]

Eight meta-analyses of genital talc exposure and ovarian cancer calculated summary relative risks that were very consistent across the publications, ranging from 1.22 to 1.35, all but one had 95% confidence intervals, indicating that women who reported talc use were at statistically significant increased risk for ovarian cancer. Similarly, the pooled analysis of eight case-control studies reported an overall odds ratio of 1.24 (95% confidence interval (CI 1.15 – 1.33), and three meta-analyses specifically evaluated genital talc exposure and risk of *serous* epithelial ovarian cancer revealing a significantly increased risk ranging from 1.24 to 1.38.[131]

---

[130] Michael Borenstein, *et al., Introduction to Meta-Analysis* (2009) at 380, attached as **Exhibit 60**; *Modern Epidemiology* at 652-653; McTiernan Rep. at 21-22; Siemiatycki Rep. at 61 ("The individual study RRs are not all necessarily statistically significant, but that is irrelevant because most individual studies did not have sufficient statistical power to detect RR in the range of 1.2-1.4. It is the statistical significance of the meta-RR, representing the combined evidence that has the requisite power and that excess RR is highly statistically significant. I place great weight upon this evidence of causality and, here, believe it to be amongst the most important findings").

[131] Berge, et al., *Genital Use of Talc and Risk of Ovarian cancer: a Meta-Analysis*, 27 European J. Cancer Prev. 248 (2018), attached as **Exhibit 61**; Penninkilampi, et al., *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*, 29 Epidemiology 41 (2018), attached as **Exhibit 62**; Taher, et al, *Systematic Review and Meta-Analysis of the Association Between perineal Use of*

These results indicate specificity as discussed, *infra*, at Section IV(G), and as depicted in the Forest-plot below:

Study	RR	Lower CI	Upper CI	← Decreased Risk ←	→ Increased Risk →
Harlow & Cramer (1992)	1.3	1.1	1.6		
Gross & Berg (1995)	1.27	1.09	1.48		
Cramer (1999)	1.36	1.24	1.49		
Huncharek (2003)	1.33	1.16	1.45		
Langseth (2008)	1.35	1.26	1.46		
Terry (2013) (Pooled)	1.24	1.15	1.33		
Berge (2018)	1.22	1.13	1.3		
Penninkilampi & Eslick (2018)	1.42	1.25	1.61		
Taher (2018)	1.28	1.2	1.37		

e. Smith Bindman meta-analysis of regular use talcum powder and high grade serous ovarian cancer (HGSOC)

The specific association between regular talcum powder use and serous ovarian cancer was further noted by Dr. Smith-Bindman in her meta-analysis of the observational data. Dr. Smith-Bindman looked at "studies that reported on regular

talc and Risk of Ovarian Cancer, Unpublished Manuscript (2018), attached as **Exhibit 63**.

talcum powder use and invasive serous cancer (or all invasive cancer if serous not reported)."[132] She found that the studies were homogenous and that the "odds of invasive serous cancer associated with regular use was 1.52 (95% CI 1.15, 1.88).[133] The results were similar when assessing the odds of all serous cancer."[134]

2. Biologic Data

Based on their review of the totality of the peer-reviewed scientific and medical literature, the PSC's experts opine that it is biologically plausible for J&J's Talcum Powder Products to increase the risk of epithelial ovarian cancer because: (1) talcum powder is capable of reaching the fallopian tubes and ovaries either

---

[132] *See* Smith-Bindman Rep. at 34.

[133] *Id.* at Figure-3 (Forest plot showing odds of ovarian cancer associated with regular use of talcum powder products and invasive serous cancer. *See also* Deposition of Rebecca Smith-Bindman, MD, February 7, 2019 and February 8, 2019 ("Smith-Bindman Dep.") at 99:15-20 (opining that women exposed to talcum powder on a regular basis had about a 50% increased risk of developing serous invasive cancer), attached as **Exhibit 64**; Siemiatycki Rep. at Figure-1 (Forest plot showing meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used TPP in the perineal area); Penninkilampi (2018) at 46 ("This meta-analysis had several strengths. None of the analyses in this review had statistically significant heterogeneity, except for non-perineal application, which indicates consistency in the direction and magnitude of the effect size between individual studies, and strengthening the reliability of the pooled effect sizes").

[134] For a complete discussion of the PSC's evidence in support of biological plausibility, see the *Plaintiffs' Steering Committee's Memorandum in Opposition to Johnson & Johnson and Johnson & Johnson Consumer, Inc.'s Motion to Exclude Plaintiffs' Experts Opinions Related to Biologic Plausibility* ("PSC Opp. Mem. Bio. Plaus.") being filed concurrently.

through migration from the perineum or through inhalation, and (2) once there, talcum powder causes chronic inflammation and oxidative stress, which increases the risk of epithelial ovarian cancer through a well-described cascade of biological and molecular processes.

These opinions are supported by the totality of long-standing and extensive peer-reviewed literature on: 1) migration of particulates within the female genital tract or through inhalation; 2) the known carcinogenic constituents in talcum powder (including asbestos, fibrous talc, heavy metals, fragrances, and other chemicals); 3) the known inflammatory properties of talcum powder; and 4) the known role inflammation and oxidative stress play in the pathogenesis of ovarian cancer. The biological evidence is far from "weak." The medical and scientific literature on each of these topics is considerable and was reviewed painstakingly by the PSC's experts in their respective fields of expertise. It is telling that J&J references very little literature in their brief, instead relying almost exclusively on the opinions of their experts who frequently contradict the conclusions of the relevant publications. When literature is cited by J&J, it is often incomplete and misleading. However, biologic data supports the PSC's contentions.

a. Biologically plausible mechanism of talcum powder and ovarian cancer: talcum powder reaches the ovaries

The PSC's experts' opinion that talcum powder can reach the fallopian tubes and ovaries when used on the perineum is based on the overwhelming body of peer-

reviewed evidence that demonstrates that substances, including particulates like talcum powder and asbestos, readily migrate from the vagina to the fallopian tubes, ovaries, and peritoneal[135] surface. These include:

- **Sperm:** Sperm move more quickly through the genital tract than would be predicted from innate motility, indicating a transport mechanism. In addition, dead sperm and inanimate sperm particles (lacking flagella) are efficiently transported upwards through the uterus and tubes.[136] This process involves directed uterine contractility that has been confirmed through research of intrauterine pressure measurements.[137]

- **Carbon particles:** Inert carbon particles were placed in the posterior vaginal fornix and observed in the fallopian tubes 28 and 34 minutes later (2 out of 3 patients tested). This research confirmed that sperm motility is not the chief factor in transport and that contractions of the uterus are likely involved in process of migration/transport of particles through the genital tract.[138]

- **Retrograde menstruation:** The transport of menstrual flow into the peritoneal cavity was first proposed by Sampson in 1927 and is now well-established as the mechanism for endometriosis initiation. The

[135] The peritoneum is the serous membrane that lines the cavity of the abdomen and pelvis and covers abdominopelvic organs.

[136] Richard E. Jones & Kristin H. Lopez, *Human Reproductive Biology* at 231-252 (3d ed. 2006), attached as **Exhibit 65**.

[137] Stefan Kissler, *et al.*, *Uterine Contractility and Directed Sperm Transport Assessed by Hystero-salpingoscintigraphy (HSSG) and Intrauterine Pressure (IUP) Measurement*, 83 Acta Obstetricia Et Gynecologica Scandinavica 369–74 (2004), attached as **Exhibit 66**.

[138] G. E. Egli & M. Newton, *The Transport of Carbon Particles in the Human Female Reproductive Tract*, 12 *Fertility and Sterility* 151–55 (1961), attached as **Exhibit 67**.

prevalence of retrograde menstruation has been described in 90% of investigated women.[139]

- **Particulate radioactive material:** Particulate radioactive material was placed in the posterior vaginal fornix. Twenty four hours later, radioactive material was present in the adnexa separate from the uterus in 2/3 of cases The authors concluded that the transit of particles from the vagina to the peritoneal cavity and the ovaries "is probably the same for many chemical substances used for hygienic, cosmetic, or medicinal purposes, many of which may have potential carcinogenic or irritating properties . . . migration of certain chemical substances could play an important aetiological role in gynaecological diseases and especially in carcinoma of the ovary."[140]

- "**Uterine peristaltic pump**"**:** Rapid and sustained sperm transport from the cervix to the fallopian tube is provided by uterine peristaltic contractions that can be visualized by vaginal sonography.[141]

- **Glove powder**: Studies have demonstrated retrograde migration of starch after gynecological examination with powdered gloves. The authors concluded that: "Consequently, powder or any other

---

[139] *See* M.J. Blumenkrantz, *et al.*, *Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis*, 57 Obstetrics and Gynecology 667–70 (1981), attached as **Exhibit 68**; *see also* J. Halme, *et al.*, *Retrograde Menstruation in Healthy Women and in Patients with Endometriosis*, 64 Obstetrics and Gynecology 151–54 (1984), attached as **Exhibit 69**.

[140] P. F. Venter & M. Iturralde, *Migration of a Particulate Radioactive Tracer from the Vagina to the Peritoneal Cavity and Ovaries*, 55 S. Afr. Med. J. 917–19 (1979), attached as **Exhibit 70**.

[141] *See* G. Kunz, *et al.*, *The Uterine Peristaltic Pump. Normal and Impeded Sperm Transport within the Female Genital Tract*, 424 Advances in Experimental Medicine and Biology 267–77 (1997), attached as **Exhibit 71**; I. Zervomanoklakis, *et al.*, *Physiology of Upward Transport in the Human Female Genital Tract*, Annals of 1101 New York Academy of Sciences 1–20 (2007), attached as **Exhibit 72**.

potentially harmful substances that can migrate from the vagina should be avoided."[142]

- **Talc**: Studies have documented the presence of talc particles in the adnexa, ovaries, and peritoneum. The authors of these studies have concluded that this occurs as a result of migration of talc particles from the vagina through the cervix, uterus, and fallopian tubes.[143] Talc has also been noted in pelvic lymph nodes which can also occur through migration, absorption, or inhalation with transport through the lymphatic system.[144]

The migration of particles and fibers, including talc, asbestos and other constituents of talcum powder, from the perineum to the upper genital tract (tubes and ovaries) is a key element in the mechanism by which J&J's Talcum Powder Products cause ovarian cancer. As outlined above and more thoroughly in the PSC's biologic plausibility briefing,[145] the evidence supporting this process is robust and accepted by the medical and scientific community. As a result, the FDA states that

---

[142] A. C. E. Sjösten, *et al., Retrograde Migration of Glove Powder in the Human Female Genital Tract*, 19 Human Reproduction 991–95 (2004), attached as **Exhibit 73**.

[143] W. J. Henderson, *et al., Talc and Carcinoma of the Ovary and Cervix*, 78 Brit. J. Obstetrics and Gynaecology 266–72 (1971), attached as **Exhibit 74**; Cramer (1999) at 160–61; D.S. Heller, *et al., The Relationship between Perineal Cosmetic Talc Usage and Ovarian Talc Particle Burden*, 174 Am. J. Obstetrics & Gynecology 1507–10 (1996), attached as **Exhibit 75**.

[144] Daniel Cramer *et al., Presence of Talc in Pelvic Lymph Nodes of a Woman with Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc*, 110 Obstetrics & Gynecology 498, 499 (2007), attached as **Exhibit 76**; McDonald, *et al., Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes*, 43 Ultrastructural Pathology 13, 21, 24 (2019), attached as **Exhibit 77**.

[145] *See* PSC Opp. Mem. Bio. Plaus.

the "potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable.[146]

The PSC's experts opine that inhalation is a secondary mechanism.[147] This mechanism is particularly important when considering asbestos and talc fibers and is well-supported in the peer-reviewed scientific literature. The IARC Monograph discussing asbestos and fibrous talc describes both inhalation and dermal contact as primary routes of exposure to the general population from cosmetic products.[148]

b. Biologically plausible mechanisms of talcum powder and ovarian cancer: chronic inflammation and oxidative stress

i. Talcum powder causes inflammation and oxidative stress

Talcum powder is known to be an inflammatory agent based on tissue reaction in animals and humans, as well as cellular effects in *in vitro* experiments. As early as 1948, in a study from the Laboratories of J&J, it was noted that "the potential

[146] *See* April 1, 2014 FDA Letter from Steven Musser to Samuel Epstein ("Musser Letter") at 5, attached hereto as **Exhibit 78**.

[147] McTiernan Rep. at 59; Plunkett Rep. at 27-28, 38, 40-41, 43-44; Plunkett Dep. at 175:19-179:24; Singh Rep. 18-19, 57-58; January 16, 2019 Deposition of Sonal Singh, MD, MPH ("Singh Dep.") at 216:5-13, attached hereto as **Exhibit 79**.

[148] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, *Arsenic, Metals, Fibres, and Dusts*, Vol. 100C: A review of Human Carcinogens (2012) at 232 ("Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powders) are the primary routes of exposure."), attached as **Exhibit 80**.

hazards of talcum as a lubricant for surgical gloves have long been a matter of concern," citing "incontrovertible evidence of the local irritant action of talcum."[149] In December, 2016, FDA finally banned talcum powder use on surgical and examination gloves due to "surgical complications related to peritoneal adhesions, and other adverse health events not necessarily related to surgery, such as inflammatory responses to glove powder."[150] In addition, talcum powder is specifically used because of its inflammatory and fibrogenic properties in a procedure called pleurodesis.[151] Concerns have also been raised due to the potential presence of talc fibers in talcum powder used in pleurodesis.[152] Granulomatous

[149] J.J. Eberl & W. L. George, *Comparative Evaluation of the Effects of Talcum and a New Absorbable Substitute on Surgical Gloves*, 75 Am. J. Surgery 493 (1948), attached hereto as **Exhibit 81**.

[150] *See* 81 Fed. Reg. 91643, 91723 (December 19, 2016) (codified at 21 C.F.R. pts. 878, 880, & 895), attached as **Exhibit 82**.

[151] *See, e.g.*, Eduardo Henrique Genofree, *Inflammation and Clinical Repercussions of Pleurodesis Induced by Intrapleural Talc Administration*, 62 Clinics (Sao Paulo) 627 (2007) ("The presence of local and systemic inflammatory alterations has been demonstrated in humans undergoing talc pleurodesis."), attached as **Exhibit 83**.

[152] *See* Ghio, *et al.*, *Talc Should Not be Used for Pleurodesis in Patients with Nonmalignant Pleural Effusions*, 164 Am. J. Respiratory & Critical Care Medicine 1741 (2001) ("Even if the product is "asbestos-free," the mechanism of cancer induction by asbestos (i.e. metal-catalyzed radical generation [oxidative stress]) is similarly pertinent to talc and the occurrence of fibrous forms of the sheet silicate itself raises issues about the clearance and long-term safety."), attached as **Exhibit 84**.

inflammation with talc and asbestos has also been reported in human ovaries.[153] Human studies examining the relationship between the biomarker MUC1 (an epithelial cell surface protein that protects against ovarian cancer) and talcum powder have also been proposed as a potential mechanism for carcinogenesis based on a case-controlled study.[154]

Animal studies have also consistently demonstrated inflammation associated with talcum powder exposure *via* inhalation and direct exposure. Although there is not a good experimental model for the development of ovarian cancer in animals,[155] inflammation can and has been consistently demonstrated. As early as 1952, samples of talc and starch were implanted in skin wounds and peritoneal cavities of animals. The authors of this study found "[t]alc was universally damaging." In contrast, the starches seemed to be relatively harmless.[156]

---

[153] *See, e.g.*, S. A. Mostafa, *et al.*, *"Foreign Body Granulomas in Normal Ovaries."* 66 Obstetrics and Gynecology 701–2 (1985) ("Noting that "it is not a new observation that talc may be found in the pelvis, nor are talc granulomas in and of themselves new observations."), attached hereto as **Exhibit 85**.

[154] *See generally* Cramer (2007).

[155] *See* Barbara C. Vanderhyden, *et al.*, *Animal Models of Ovarian Cancer*, 1 Reproductive Biology & Endocrinology 67 (2003) ("[T]he low incidence and/or the length of time required for the appearance of tumors in all of these models render them poorly feasible for experimental studies of ovarian carcinogenesis. . . Epithelial inclusion cysts may occur following 'inflammation caused by carcinogens or chemical irritants like talcum powder.'"), attached hereto as **Exhibit 86**.

[156] Graham & Jenkins, *Value of Modified Starch as a Substitute for Talc*, 1 Lancet 590–91 (1952), attached hereto as **Exhibit 87**.

Moreover, in the National Toxicology Program animal inhalation study using non-asbestiform, cosmetic grade talc, toxic inflammatory effects of talcum powder exposure included chronic inflammation, alveolar epithelial hyperplasia, squamous metaplasia and squamous cysts, and interstitial fibrosis of the lung, as well as carcinogenic activity in some organs, including lungs and adrenal glands.[157] In addition, various abnormal findings related to inflammation have been reported in animals following exposure to talcum powder, such as "conversion from a single layer epithelium to a multilayered one with extremely abnormal cells and mitotic activity,"[158] "papillary transformation,"[159] "unfavorable effects on the female genital system, particularly on ovaries and fallopian tubes."[160] A meta-analysis of an impressive 64 publications reported on the association between exposure to mineral particles (including asbestos) and oxidatively damaged DNA in tissues of animals.[161]

---

[157] NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) (NonAsbestiform) in F344/N.Rats and B6C3Fl Mice (Inhalation Studies), 1993, attached as **Exhibit 88**.

[158] J.Graham & R. Graham, *Ovarian Cancer and Asbestos*, 1 *Environmental Research* 115–28 (1967), attached hereto as **Exhibit 89**.

[159] T.C. Hamilton, *et al.*, *Effects of Talc on the Rat Ovary*, 65 Br. J. Experimental Pathology 101–665 (1984), attached hereto as **Exhibit 90**.

[160] Nadi Keskin, *et al.*, *Does Long-Term Talc Exposure Have a Carcinogenic Effect on the Female Genital System of Rats? An Experimental Pilot Study*, 280 Archives Gynecology & Obstetrics 925–31 (2009), attached hereto as **Exhibit 91**.

[161] Danielsen Moller & Roursgaard Jantzen, *Oxidatively Damaged DNA in Animals Exposed to Particles*, 43 Critical Reviews in Toxicology 96–118 (2013), attached hereto as **Exhibit 92**.

In vitro studies also document inflammatory and pro-carcinogenic biologic effects in cell cultures exposed to talcum powder. These studies include Shukla[162] (demonstrating genotoxicity in both asbestos and non-fibrous talc), Buz'Zard[163] (demonstrating aberrant ROS [reactive oxygen species] and neoplastic transformation), Akhtar[164] (demonstrating induced cytotoxicity, oxidative stress, and apoptosis), and Akhtar[165] (demonstrating toxicity mediated through oxidative stress). Saed and his colleagues expand this body of literature by exposing 5-6 cell lines including normal fallopian tube and ovarian cells, as well as ovarian cancer cells, to *Johnson's Baby Powder*, finding alteration in the redox state indicating

---

[162] Arti Shukla, *et al.*, *Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity*, 41 Am. J. Respiratory Cell & Molecular Biology 114–23 (2009), attached hereto as **Exhibit 93**.

[163] Buz'Zard & Lau, *Pycnogenol reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures*, 21 Phytother. Res. 579, 585 (2007) ("The data show that talc is capable of increasing cell proliferation, inducing neoplastic transformation of both the normal stromal and epithelial ovarian cells *in vitro*; and increasing ROS generation in these cells as well as the PMN cells."), attached as **Exhibit 94**.

[164] M.J. Akhtar, *et al.*, *Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells*, Envtl. Tox. 394, 404 (2014) (talc particles "significantly induced cytotoxicity, oxidative stress, and apoptosis in human lung epithelial cells"), attached hereto as **Exhibit 95**.

[165] M. J. Akhtar, *et al.*, *The Primary Role of Iron-Mediated Lipid Peroxidation in the Differential Cytotoxicity Caused by Two Varieties of Talc Nanoparticles on A549 Cells and Lipid Peroxidation Inhibitory Effect Exerted by Ascorbic Acid*, 24 Tox. in Vitro 1139–47 (2010), attached hereto as **Exhibit 96**.

oxidative stress, elevation in CA-125 levels, enhanced cell proliferation, inhibited apoptosis, changes in gene expression, and inducement of SNPs (single nucleotide polymorphisms) in a dose-responsive fashion.[166]

ii. Talcum powder cause inflammation and oxidative stress

Inflammation and oxidative stress are considered a "hallmark" of carcinogenesis, generally, and play a key role in the pathogenesis of ovarian cancer, specifically. Both concepts are extensively reported in the medical and scientific literature. In an article from 2001, Balkwill and Mantovani reviewed multiple cancers associated with various inflammatory conditions, specifically reporting talc as an "inflammatory stimulus/condition" for the "association of inflammation and ovarian cancer risk."[167]

A more recent review, *Hallmarks of Cancer: The Next Generation*, states that "since 2000, research on the intersections between inflammation and cancer pathogenesis has blossomed, producing abundant and compelling demonstrations of the functionally important tumor-promoting effects that immune cells – largely of

---

[166] Nicole M. Fletcher, *et al.*, *Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer*, 20 Reproductive Sciences 1 (2019), attached hereto as **Exhibit 97**.

[167] *See, e.g.*, F. Balkwill & A. Mantovani, *Inflammation and cancer: back to Virchow?*, 357 Lancet 539, 539 (2001) ("increased risk of malignancy is associated with the chronic inflammation caused by chemical and physical agents"), attached hereto as **Exhibit 98**.

the innate immune system – have on neoplastic progression. Inflammation is described as fostering multiple hallmark functions."[168] Furthermore, numerous other peer-reviewed publications describe the importance of inflammation and oxidative stress in carcinogenesis.[169] Health Canada also concluded, in their recent draft

[168] D. Hanahan & R.A. Weinberg, *Hallmarks of Cancer: The Next Generation*, 144 Cell 646, 659 (2011) ("[I]nflammatory cells can release chemicals, notable reactive oxygen species, that are actively mutagenic for nearby cancer cells, accelerating their genetic evolution toward states of heightened malignancy."), attached hereto as **Exhibit 99**.

[169] *See, e.g.*, L. Coussens & Zena Webb, *Inflammation and Cancer*, 420 Nature 860-867, at Table 1 (2002) (noting that "inflammatory cells have powerful effects on tumor development. Tumor development and progression are accelerated inevitably by inflammation caused from foreign bodies, and that reactive oxygen species derived from inflammatory cells are one of the most important genotoxic mediators to accelerate the process."), attached hereto as **Exhibit 100**; Liou & Storz, *Reactive oxygen species in cancer*, 44 Free Radical Research 479, 479 (2010) ("Elevated rates of ROS have been detected in almost all cancers… ROS in cancer are involved in cell cycle progression and proliferation, cell survival and apoptosis."), attached hereto as **Exhibit 101**; Grivennikov, *et al., Immunity, Inflammation, and Cancer*, 140 Cell 883, 883 (2010) ("A role for inflammation in tumorigenesis is now generally accepted, and it has become evident that an inflammatory microenvironment is an essential component of all tumors, including some which a direct causal relationship with inflammation is not yet proven."), attached as **Exhibit 102**; Reuter, *et al., Oxidative stress, inflammation, and cancer: How are they linked?*, 49 Free Radical Biol. Med. 1603-1616 (2011) ("Cancer is a multistage process defined by at least three stages: initiation, promotion, and progression. Oxidative stress interacts with all three stages of this process. Initiation (DNA damage by introducing gene mutations and structural alterations of DNA); Promotion (Abnormal gene expression and interference with communication, resulting in increase in cell proliferation and decrease in apoptosis); Progression (further DNA alterations)… Considerable evidence has demonstrated that ROS are involved in the link between chronic inflammation and cancer."), attached as **Exhibit 103**; Fernandes, *et al., The Role of the Mediators of Inflammation in Cancer Development*, 21 Pathol. Oncol. Res. 527, 527 (2015) ("A range of inflammation

assessment, that [t]here is support for an association of inflammation and increased risk of ovarian cancer."[170]

Moreover, there is considerable literature that exists linking inflammation and oxidative stress with epithelial ovarian cancer, specifically. In 1999, Ness reported on the role of inflammation in ovarian epithelial cancer, implicating talc and asbestos exposure as sources of carcinogenic inflammation.[171] Ness described the process as involving rapid cell division, DNA excision and repair, oxidative stress, and high concentrations of cytokines and prostaglandins, all of which are established promoters of mutagenesis. Additional literature has since confirmed and expanded the understanding of the inflammatory mechanisms originally proposed by Ness.[172]

---

mediators act to create a favorable microenvironment for the development of tumors.), attached hereto as **Exhibit 104**; Kiraly, *et al., Inflammation, DNA Damage and Mutations In Vivo*, 11 PLO Genetics 1, 2 (2015) (Chronically inflamed tissues are at risk for mutagenesis and malignant transformation), attached hereto as **Exhibit 105**.

[170] Health Canada Assessment at 18.

[171] Roberta B. Ness & Carrie Cottreau, *Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer*, 91 J. Nat'l Cancer Inst. 1459, 1463 (1999), attached hereto as **Exhibit 106**; In an internal document, J&J found this evidence "compelling." *See* September 30, 2004 Faxed document from Richard Zazenski, Director Product Safety to Bill Ashton (Bates JNJ 000000704 - JNJ 000000709), attached as **Exhibit 107**; *see also* Ness (2000).

[172] *See* Freedman, *et al., Peritoneal inflammation – A microenvironment for Epithelial Ovarian Cancer (EOC)*, 2 J. Translational Med. 1, 4 (2004), attached as **Exhibit 108**; Shan & Liu, *Inflammation: A hidden path to breaking the spell on ovarian cancer*, 8 Cell Cycle 3107, 3110 (2009) ("Increasing evidence suggests that inflammation contributes significantly to the etiology of EOC."), attached as **Exhibit 109**; Trabert, *et al., Pre-diagnostic levels of inflammation markers and risk of*

In an authoritative treatise published in 2016 under auspices of the Institute of Medicine (IOM), the Committee on the State of the Science in Ovarian Cancer Research identified inflammation as a risk for epithelial ovarian cancer, and found that talcum powder and asbestos are specific inflammatory factors associated with ovarian cancer.[173]

Furthermore, Dr. Saed published his review article in *Gynecologic Oncology* in 2017, "*Updates in the role of oxidative stress in the pathogenesis of ovarian cancer*," describing in detail the essential role of oxidative stress in ovarian cancer.[174]

---

ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial, 135 *Gynecologic Oncology* 297, 298, 309 (2014) ("Epidemiological evidence implicates chronic inflammation as a central mechanism in the pathogenesis of ovarian cancer."), attached as **Exhibit 110**; Rasmussen, *et al., Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Tumors: A Pooled Analysis of 13 Case-Control Studies*, 185 Am. J. Epidemiology 8-20 (2017) (a pooled analysis of 13 case-control studies finding an association between PID and the risk of ovarian tumors is biologically plausible and could be explained by the inflammation hypothesis.), attached as **Exhibit 111**.

[173] *See* National Academies of Science, Engineering and Medicine, *Ovarian Cancers: Evolving Paradigms in Research and Care* ("IOM") at 110 (2016), attached as **Exhibit 112**. The study was commissioned by Congress, and funded by the CDC (holding that talc is chemically similar to asbestos and can cause an inflammatory response. The use of perineal talcum powder has been associated with a 20 to 30 percent increased risk of ovarian cancer, although it also has been shown to vary by histologic subtype (Cramer *et al.,* 2015; Terry *et al.,* 2013)).

[174] Saed *et al., Updates on the role of oxidative stress in the pathogenesis of ovarian cancer*, Gynecologic Oncology 145: 595-602, at 596-97 (2017), attached as **Exhibit 113**.

J&J's expert, Dr. Birrer, agrees that authors of review articles like this one in reputable journals are generally felt to be experts in the field.[175]

Finally, in an even more recent review, the authors concluded that *talc exposure* is a cause of inflammation in the ovaries and/or fallopian tubes. The mechanism is through oxidative stress and "ROS exposure that could potentially lead to epithelial cells in the ovary and FT [fallopian tubes] undergoing transformative changes, as has been demonstrated for ovarian surface epithelium cells grown in 3D culture."[176]

c. Biologically plausible mechanisms of talcum powder and ovarian cancer: talcum powder contains known and probable carcinogens

There is credible evidence from Johnson & Johnson's own testing results, Imerys Talc America's test results, peer-reviewed scientific literature, as well as Drs. Longo and Rigler's testing that *Johnson's Baby Powder* and *Shower-to-Shower* have historically contained asbestos and fibrous talc.[177] These components are universally

[175] *See* March 29, 2019 Deposition of Michael Birrer, M.D., Ph.D. ("Birrer Dep.") at 394:11-17, attached hereto as **Exhibit 114**.

[176] *See* Savant *et al., The Role of Inflammation and Inflammatory Mediators in the Development, Progression, Metastasis, and Chemoresistance of Epithelial Ovarian Cancer*, 10 Cancers1-30 at Figure 1 (2018), attached hereto as **Exhibit 115**.

[177] For a complete discussion of the evidence regarding the presence of asbestos, fibrous talc, nickel, chromium, and cobalt, please see the *Plaintiffs' Steering Committee's Memorandum in Opposition to Johnson & Johnson and Johnson & Johnson Consumer, Inc.'s Motion to Exclude Plaintiffs' Experts' Asbestos-Related Opinions* and *Plaintiffs' Steering Committee's Memorandum in Opposition to*

accepted as potent human carcinogens and identified as Group 1 carcinogens for cancer in humans, including ovarian cancer.[178]

As noted above, the mechanism of inflammation by which asbestos and talc fibers causes cancer is well-described in the scientific literature. IARC proposed direct and indirect mechanisms, both associated with inflammation. In the direct mechanism, mineral fibers are shown to generate free radicals that directly induce genotoxicity as assessed by DNA breaks and oxidized bases in DNA. In the indirect mechanism, asbestos fibres induce macrophage activation and persistent inflammation that generate reactive oxygen and nitrogen species contributing to tissue injury, genotoxicity, and epigenetic alterations. Persistent inflammation and chronic oxidative stress have been associated with the activation of intracellular signaling pathways, resistance to apoptosis, and stimulation of cell proliferation.[179] Defense Expert Brooke Mossman, in her 2018 review article on *in vitro* mechanisms for the carcinogenesis of "EMPs" (elongated mineral particles or fibers), confirms the mechanisms outlined by IARC in 2012, whereby long EMPs appeared to be promoters of cancers via a number of mechanisms such as inflammation, generation

---

Johnson & Johnson and Johnson & Johnson Consumer, Inc.'s Motion to Exclude Plaintiffs' Experts Opinions Regarding Alleged Heavy Metals and Fragrances in Johnson's Baby Powder and Shower to Shower, being filed concurrently and both of which are incorporated herein by reference.

[178] IARC (2012).

[179] IARC (2010) at 397-98; IARC (2012) at 288.

of oxidants, and instigation of cell division through epigenetic and signaling cascade processes.[180]

In addition to asbestos and fibrous talc, heavy metals (most notably, nickel, chromium, and cobalt) are found in Talcum Powder Products. Nickel and chromium are considered known carcinogens (Group 1) according to IARC; chromium is considered a possible carcinogen (Group 2B) by IARC.[181] In addition, Defendants actually add chemicals to their Talcum Powder Products that are suspected carcinogens, including styrene, a well-recognized toxic chemical recognized by IARC as Group 2A (probably carcinogenic).[182] As part of the expert review, the IARC Working Group evaluated relevant data, including genetic effects, oxidative stress, DNA damage and repair, and cell proliferation.

The Agency for Toxic Substances and Disease Registry (ATSDR) has also described the carcinogenic mode of action (or mechanism) for nickel: "The available evidence suggests that, mechanistically, nickel carcinogenicity is probably the result of genetic factors and/or direct (e.g., conformational changes) or indirect (e.g., generation of oxygen radicals) epigenetic factors. Additionally, certain nickel

---

[180] Brooke T. Mossman, *Mechanistic in Vitro Studies: What They Have Told Us about Carcinogenic Properties of Elongated Mineral Particles (EMPs)*, 361 Tox. & Applied Pharmac. 62-67 (2018), attached hereto as **Exhibit 116**.

[181] IARC (2012).

[182] *Id*.

compounds promote cell proliferation, which would convert repairable DNA lesions into nonrepairable mutations. Nickel is considered to be genotoxic…"[183] And according to the ATSDR, chromium (VI), chromium (V), and chromium (IV) "have all been shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species…"[184] "It is believed that the formation of these radicals, which leads to oxidative stress, may be responsible for many of the deleterious effects of chromium on cells…"[185] ATSDR describes the inflammatory mechanism of action for cobalt to include the following: "Exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage…"[186] The NTP has listed chromium (VI)[187] and

[183] US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR), *Toxicological Profile for Nickel* (2005) at 155.

[184] US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR), *Toxicological Profile for Chromium* (2012) at 281.

[185] *Id.* at 282.

[186] ATSDR (2005) at 154.

[187] US Department of Health and Human Services, National Toxicology Program, *Report on Carcinogens: Monograph on Cobalt and Cobalt Compounds that Release Cobalt Ions in vivo* (2016).

nickel[188] as "known to be human carcinogens," while cobalt is listed as "reasonably anticipated to be human carcinogens."[189]

In sum, there is abundant and reliable medical and scientific literature supporting the PSC's experts' opinions that there is a biologically plausible mechanism by which talcum powder causes ovarian cancer because: (1) talcum powder can migrate or translocate to the fallopian tubes, ovaries and peritoneal surfaces from perineal use, and when inhaled, can enter the bloodstream and lymphatic system and then travel to the ovaries, and (2) once there, induce chronic inflammation and oxidative stress, which increases the risk of ovarian cancer.

B. THE MEDICAL CONSENSUS: TALCUM POWDER IS A RISK FACTOR EPITHELIAL FOR OVARIAN CANCER

1. The clinical definition of "risk factor"

In clinical medicine, the term "risk factor" is often used to describe something that increases the chance of developing a disease.[190] An "evidence-based medicine" approach for doctors is very similar to a Bradford-Hill analysis, as "medical decisions should be based on quality evidence."[191] Cause and risk factor are often

---

[188] *Id*.

[189] *Id*.

[190] *See* National Cancer Institute, *NCI Dictionary of Cancer Terms*, available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/risk-factor.

[191] Wendy R. Brewster, *Epidemiology of Commonly Used Statistical Terms and Analysis of Clinical Studies*, Clinical Gynecologic Oncology at 579-585 (9th ed. 2017), attached hereto as **Exhibit 120**.

used interchangeably, assuming there exists a plausible biological mechanism to explain the association.[192] This methodology for determining cancer causality merges traditional epidemiology, molecular research, and public health decision-making.[193]

In addition to epidemiological studies reporting a consistent association of talcum powder use and the risk of ovarian cancer, there are numerous peer-reviewed medical publications, particularly in recent years, describing and listing talcum powder use as a risk factor for epithelial ovarian cancer, thus incorporating mechanism. In addition to talcum powder and asbestos exposure, other risk factors that have been linked to epithelial ovarian cancer include increasing age, nulliparity,

---

[192] *See* February 4, 2019 Deposition of Daniel L. Clarke-Pearson, M.D. ("Clarke-Pearson Dep.") at 80:3-5 ("They're virtually the same. A risk factor describes a cause. It does not affect every woman that has that risk factor."), attached hereto as **Exhibit 121**. *See also* Smith Rep. at 19 ("For a doctor treating patients, knowledge of risk factors and causes of diseases are important for diagnosis, prevention, and treatment of the diseases. In essence, risk factors (associated with a health outcome) can be considered causal when the biological and molecular mechanisms for this relationship are known or predictable based on scientific research."); Wolf Rep. at 3-4 ("A causative risk factor is one that increases the chances of developing a disease by means of a known or predictable mechanism. In other words, it is more than a mere association.").

[193] Paolo Vineis, *et al.*, *Causality in Cancer Research: A Journey through Models in Molecular Epidemiology and Their Philosophical Interpretation*, 14 Emerging Themes in Epidemiology 7 (2017) ("[C]ausal reasoning is based on both 'evidence of difference-making' (e.g. associations) and on 'evidence of underlying biological mechanisms'. . . .This is important not only to understand cancer etiology, but also to design public health policies that target the right *causal* factors at the macro-level."), attached as **Exhibit 122**.

infertility, endometriosis, obesity, polycystic ovarian syndrome, use of an intrauterine device, history of pelvic inflammatory disease, and cigarette smoking (for mucinous carcinoma). Protective factors (*i.e.*, those factors associated with a decreased risk of epithelial ovarian cancer) include previous pregnancy, history of breastfeeding, oral contraceptives, and tubal ligation.[194]

It is important to note that risk factors can interact with each other or act independently. They can act in a cumulative, additive, and/or synergistic fashion.[195] Talcum powder usage is often referred to as a "lifestyle risk factor" and therefore, a modifiable and preventable cancer cause.

2. The Institute of Medicine and the Medical Literature Recognize Talcum Powder as a Risk Factor for Epithelial Ovarian Cancer

There are multiple peer-reviewed publications that recognize the genital use of talcum powder as a risk factor for epithelial ovarian cancer. Some examples follow.

- **Hunn and Rodriguez (2012),** in a review article titled "Ovarian Cancer: Etiology, Risk Factors, and Epidemiology" include "perineal talc exposure" as an "inflammatory risk factor," describing the "[e]vidence demonstrating an association between talc use and an increased risk of ovarian cancer suggests that

[194] *See* Wolf Rep. at 4.

[195] Song Wu, *et al.*, *Evaluating Intrinsic and Non-Intrinsic Cancer Risk Factors*, 9 Nature Commc'n 3490 (2018) ("Non-intrinsic and intrinsic risk factors often do not act independently as we have highlighted, and the most likely scenario is that they cooperate to cause cancer "); attached as **Exhibit 123**.

environmental toxins can enter the lower genital tract and migrate upward through the uterus and fallopian tubes to enter the peritoneal cavity and act as ovarian carcinogens."[196]

- **Mallen and colleagues (2018):** in a review titled, "Risk Factors for Ovarian Carcinoma," included in its risk factor chart talcum powder as a "Lifestyle Risk Factor" for all serous, endometrioid and clear cell carcinomas.[197]

- **Park *et al.* (2018):** described the increased risk in the African-American population: "In particular, talc powder use is highly prevalent in the African-American community and has been found to be associated with increased risk of ovarian cancer in this and other studies."[198]

- In a textbook chapter titled Ovarian Cancer Screening and Prevention, the authors described talc use as a "lifestyle factor," stating that the "[u]se of talc in the genital area has been consistently shown to increase the risk of OC and therefore is not recommended."[199]

- The Institute of Medicine (IOM) in the "state of the science" treatise on ovarian cancer identified talc and asbestos as inflammatory

[196] Hunn and Rodriguez (2012), attached as **Exhibit 124**.

[197] Mallen *et al.* (2018), attached as **Exhibit 125**.

[198] Park *et al.* (2018), attached as **Exhibit 126** (noting "The risk associated with serous ovarian cancer in women with a history of multiple conditions was higher than individual associations observed in any one gynecologic condition. This observation may suggest a possible additive or synergistic effect on tumorigenesis influenced by the pro-inflammatory milieu from an increased burden in the number of benign conditions. Increased risk of serous carcinoma in women with other pro-inflammatory risk factors has been reported, *most notably in talc users*.").

[199] Eeles, et al. *Cancer Prevention and Screening: Concepts, Principles and Controversies*, Chapter 23 (2018), attached as **Exhibit 127**.

factors associated with ovarian cancer in the biological plausibility section.[200]

3. Ovarian cancer subtypes

High-grade serous carcinoma is the most common and most lethal subtype of epithelial ovarian cancer, and the one that is most associated with the perineal use of talcum powder. It is customary to refer to the various histologic subtypes, as well as fallopian tube and peritoneal cancer as a single entity, albeit distinguishing when appropriate. For example, the National Cancer Institute (NCI) treats Ovarian, Fallopian Tube, and Primary Peritoneal Cancer as a single cancer, as does the American College of Obstetrics and Gynecology (ACOG). A recent review seminar published in the Lancet (2019), titled "Epithelial ovarian cancer" provides a further example. Although the distinct histological subtypes are discussed in this article, epithelial ovarian cancer is addressed as a whole, including risk factors.[201]

The epidemiological literature commonly does not distinguish between subtypes, nor do treatises by governmental agencies (*e.g.* IARC, Health Canada, FDA). Remarkably, J&J cherry-picks a recent publication in the New England Journal of Medicine, titled "Mucinous Ovarian Cancer," as their primary example

[200] *See* IOM (2016).

[201] Lheureux, *et al.*, *Epithelial Ovarian Cancer*, 393 Lancet 1240–53 (2019), attached as **Exhibit 128**.

of an article that *did not list talc as a risk factor*.[202] J&J did not cite the title of the article in the footnote; did not furnish the article to the court in their exhibits; failed to mention that mucinous ovarian cancer represents only 3% of EOC; and did not include the fact that mucinous ovarian cancer is the least studied subtype in regards to its association with talcum powder usage (likely due to its rarity). This article does not pertain to the other 97% of Epithelial Ovarian Cancer.

C. OTHER COURTS' CONSIDERATION OF RELIABILITY OF TALC AND OVARIAN CANCER SCIENCE

In its brief, J&J has emphasized the two (2) state court decisions in *Carl v Johnson & Johnson* (N.J Super Ct. Law. Div, September 2, 2016) and *Echeverria v. Johnson & Johnson, et al.* (*In re Johnson & Johnson Talcum Powder* (Cal. Super. Ct. Oct 20, 2017).[203] However, these are not the only two (2) cases to have considered the reliability of the general causation evidence. Three (3) other courts—a federal court in South Dakota, a state court in Missouri, and a state court in Georgia—have considered the issue of general causation, both under a *Daubert* and similar state-court standard, and have denied J&J's motion. Each of these is briefly described below. While the PSC believes that the courts in Missouri and South Dakota reached the correct result under *Daubert* and that their reasoning should be

[202] Morice, *et al.*, *Mucinous Ovarian Cancer*, 380 New Eng. J. Med. 1256 (2019), attached as **Exhibit 129**.

[203] Defs.' Mem. at 4.

followed, none of those cases had the experts or evidence that this Court has before it.

- ***Berg v. Johnson & Johnson:***[204] *Berg* was tried to a jury in 2013 in the U.S. District Court for the District of South Dakota, and the testimony of the plaintiff's general causation experts, based on the then existing evidence, survived J&J's *Daubert* challenges in full and a copy of that order is attached.[205] Briefly, the plaintiff in *Berg* presented evidence that "the association between use of cosmetic talc powder in the genital area and ovarian cancer with regard to the likelihood that this is cause-and-effect."[206] As here, J&J argued that the epidemiology expert in that case could not opine as he did because he did not interpret the epidemiology studies properly and because the epidemiologists' interpretation of odds ratios was unreliable. J&J challenged that experts' methodology alleging that his opinions were "speculative, untested, and unreliable" as to biological plausibility.[207] The court, applying *Daubert*, concluded that J&J was really criticizing the epidemiologist's' "results, not his methodology,"[208] and that "[a]ny gaps or limitations in [toxicology] can be presented to the jury."[209] There, the court properly ruled that the areas of expert disagreement was a jury question, and not a question of reliability which the court must resolve under Daubert.

[204] *Deane Berg v. Johnson & Johnson, et al.*, Case No. 4:09-cv-04179-KES, (D.S.D).

[205] In *Berg*, the plaintiff's expert Dr. John Godleski was offered as an expert to testify on identifying foreign particles in human tissue, and the trial court also allowed his testimony. He identified talc in the plaintiff's ovarian tissue.

[206] *See Daubert* Memorandum and Order at 7, attached as **Exhibit 130**.

[207] *Id.* at 23-27.

[208] *Id.* at 13.

[209] *Id.* at 27.

- **Missouri Cases**:[210] There have been several cases tried to verdict in Missouri. In each case, J&J made the same arguments as it does here: that plaintiffs' experts' testimony and opinions are "not accepted" by the scientific community or regulatory bodies[211] that their causation methodology was unreliable, with a focus on dose response, biological plausibility, and talc migration.[212] The Missouri's expert witness standard is codified at Mo. Rev. Stat. § 490.065, and it substantively mirrors Fed. R. Evid. 702 concerning the admissibility of expert witness testimony. The Missouri court rejected these arguments stating that these are jury questions.[213]

- ***Carl v. Johnson & Johnson***:[214] As it does here, in *Carl*, J&J argued that the Bradford-Hill aspects could not be reliably met. The trial judge in *Carl* limited his analyses to just the epidemiologists and, although he criticized them for not considering biologic evidence, his opinion does not address the biologic evidence *plaintiffs presented from those disciplines.* While the expert epidemiologists for both-sides applied the *same* methodology, the court sided with J&J and weighed the cohort studies differently than plaintiffs' experts did, improperly substituting *his own* judgment for that of the jury. More fundamentally, however, there is absolutely no overlap whatsoever between a single challenged expert in *Carl* and any of PSC's experts in the MDL *and* the scientific landscape has evolved

---

[210] *Jacqueline Fox vs. Johnson & Johnson, et al.,* Cause No. 1422-CC09012-01; (reversed on other grounds); *Gloria Ristesund vs. Johnson & Johnson, et al.,* Cause No. 1422-CC09012-01; (reversed on other grounds); *Deborah Giannecchini vs. Johnson & Johnson, et al,* Cause No. 1422-CC09012-01(on appeal); *Nora Daniels vs. Johnson & Johnson, et al.* Cause No. 1422-CC09326-01; *Lois Slemp vs. Johnson & Johnson, et al.,* Cause No. 1422-CC09326-01 (on appeal); *Gail Lucille Ingham, et al. vs. Johnson & Johnson, et al.,* Cause No. 1522-CC10417-01; *Michael Blaes, et al. vs. Johnson & Johnson, et al.,* Cause No. 1422-CC09326-01.

[211] *Id.* at 30.

[212] *Id.* 33-44.

[213] *See, e.g., Blaes v Johnson & Johnson*, 1422-CC0936-10, Order (June 12, 2017), **Exhibit 131**.

[214] Carl v Johnson & Johnson, No. ATL-L-6540-14, 2016 WL 4580145, at *19 (N.J.Super.L. Sep. 02, 2016), appeal pending.

significantly in the three (3) years since that court considered the evidence. Since 2016, for example, numerous meta-analysis have been performed and each found a positive association between perineal use of talc powder and ovarian cancer, including in a meta-analysis of cohort studies. In fact, as set forth herein, Health Canada has reviewed all of the evidence and stated that the totality of the evidence—including evidence Judge Johnson never saw -- shows a "causal effect." Moreover, Judge Johnson did not consider the implications (for example) of the presence of asbestos (a known carcinogen) on the biologic plausibility of Talcum Powder Products causing ovarian cancer.

- ***In Re: Johnson & Johnson Talcum Powder* (JCCP 4872)**:[215] J&J lost its *Sargon* (California's version of *Daubert*) motions after a hearing on general causation and, among others, Dr. Siemiatycki testified on general causation. Following trial, however, the Court granted J&J's motions for judgment notwithstanding the verdict and, alternatively, for a new trial. The issues on appeal are primarily case specific, *i.e.* whether plaintiffs' specific-causation expert was required to completely rule out *all other possible causes* of her ovarian cancer, and whether the case-specific expert had opined that plaintiff's cancer was caused by some unknown factor.

- ***Brower v. Johnson & Johnson*:**[216] Georgia is the most recent court to consider the general causation issue and explicitly did so under *Daubert*. In an order dated March 16, 2019, the Court denied J&J's motion stating that where the expert detailed their methodology, "defendants' contentions go to the credibility of the testimony, not its admissibility.[217]

[215] *In Re: Johnson & Johnson Talcum Powder Cases*, No. BC628228, 2017 (plaintiff Eva Echeverria only).

[216] *Brower v. Johnson & Johnson*, No. 16-EV---5534-E (Ga. Fulton Co).

[217] *See, e.g, Brower v J&J*, No. 16-EV---5534-E (Ga. Fulton Co.) Order, March 26, 2019, attached hereto as **Exhibit 132**.

IV. ARGUMENT

A. LEGAL STANDARDS FOR ADMISSIBILITY OF EXPERT GENERAL CAUSATION OPINIONS

The PSC incorporates the *Plaintiffs' Steering Committee's Omnibus Brief Regarding Daubert Legal Standards and Scientific Principles for Assessing General Causation*[218] and highlights the following important points of particular relevance to the outcome this motion:

First, Fed. R. Evid. 702 has "a liberal policy of admissibility."[219] Exclusion of expert testimony is only appropriate when such testimony qualifies as irrelevant or "junk science"[220] Otherwise, the trial court should cede complex issues to the jury and rely on the traditional safeguards of the adversary system—active cross-examination, presentation of contrary and competing expert testimony—rather than exclude from juror scrutiny for fear that they will not grasp its complexities or satisfactorily weigh its inadequacies.[221]

Second, differing and competing expert opinions, precisely what J&J has presented to the Court, are traditionally left for the jury. The *Daubert* analysis

---

[218] ECF Doc. 9732 (hereinafter "*PSC's Omnibus Brief*").

[219] *Geiss v. Target Corp.*, No. CIV. 09-2208 RBK/KMW, 2013 WL 4675377, at *4 (D.N.J. Aug. 30, 2013) (citing *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008)) (other citations omitted).

[220] *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 596, 113 S. Ct. 2786 (1993).

[221] *In re TMI Litig.*, 193 F.3d 613, 692 (3d Cir. 1999).

focuses on the methodology underlying an expert's opinion, not the expert's conclusions.[222] Therefore, the focus of admissibility under *Daubert* is the reliability of the experts' methods, not their correctness.[223] The trial court is not empowered "to determine which of several competing scientific theories has the best province."[224] As long as the expert's testimony falls within "the range where experts may reasonably differ," then it is up to the jury to decide among the competing views.[225]

Third, it is important to emphasize that all studies have "flaws" in the sense of limitations that add uncertainty about the proper interpretation of the results."[226] Where an opinion is challenged based on there being "flaws" in a study, the remedy

---

[222] *Daubert*, 509 U.S at 595.

[223] *Id*. at 585. *See also Beech Aircraft Corp. v. Rainey*, 488 U.S. 153, 1969 (1988); Fed. R. Evid. 702.

[224] *Milward v. Acuity Specialty Prod. Grp., Inc.*, 639 F.3d 11, 15 (1st Cir. 2011) (internal quotation marks and citations omitted)

[225] *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 153, 119 S. Ct. 1167, 143 L. Ed. 2d 238 (1999); *In re: Tylenol (Acetaminophen) Mktg., Sales Practices, & Prod. Liab. Litig.*, No. 2436, 2016 WL 4039286, at *2 (E.D. Pa. July 28, 2016) ("Fed. R. Evid. 702 and *Daubert* put their faith in an adversary system designed to expose flawed expertise."); *United States v. Mitchell*, 365 F.3d 215, 244–45 (3d. Cir. 2004) (citations omitted) ("As long as an expert's scientific testimony rests upon 'good grounds, based on what is known,' it should be tested by the adversary process—competing expert testimony and active cross–examination—rather than excluded from jurors' scrutiny for fear that they will not grasp its complexities or satisfactorily weigh its inadequacies.").

[226] *Ref. Man.* at 552.

is not preclusion under *Daubert*; rather, the alleged flaws go to the weight of [the expert witness's] opinion, not its admissibility.[227] The Court also should not reject expert testimony because statements in published articles may "cast doubt on [the expert's] position;" this would "set the bar too high."[228]

Fourth, causal inference is a matter of judgment about the totality of the scientific evidence. "Drawing causal inference . . . requires judgment and searching analysis based on biology, of why a factor or factors may be absent despite a causal relationship, and vice versa."[229] As noted in the *Reference Manual*: "Although the drawing of causal inference is informed by scientific expertise, it is not a determination that is made by using an algorithmic methodology."[230] As this judgment is a scientific determination, it can evolve "as new evidence develops" because "the scientific enterprise must always remain open to reassessing the validity of past judgments."[231] The judgment of whether to draw a causal inference can lead to disagreement amongst experts in the field.[232] In the end, deciding whether

---

[227] *See In re Avandia Mktg., Sales Practices & Prod. Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576, at *9 (E.D. Pa. Jan. 4, 2011).

[228] *Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co.*, 161 F.3d 77, 85 (1st Cir. 1998).

[229] *Ref. Man.* at 600.

[230] *Id.*

[231] *Id.* at 598.

[232] *See, e.g., In re Neurontin*, 612 F. Supp. 2d at 149 (causation supported by biologic plausibility notwithstanding the "robust debate in the scientific community"

associations are causal typically is not a matter of statistics alone, but also rests on scientific judgment."[233] J&J's brief is silent on this essential point.

Fifth, a causal inference requires an examination of the totality of the scientific evidence. "Scientific inference typically requires consideration of numerous findings, which, when considered alone, may not individually prove the contention."[234] This is how science outside of the courtroom functions. There is simply no definitive check-list or magic formula for making scientific judgments. As explained in the *Reference Manual*:

> It appears that many of the most well-respected and prestigious scientific bodies (such as the International Agency for Research on Cancer (IARC), the Institute of Medicine, the National Research Council, and the National Institute for Environmental Health Sciences) consider all the relevant available scientific evidence, taken as a whole, to determine which conclusion or hypothesis regarding a causal claim is best supported by the body of evidence. In applying the scientific method, scientists do not review each scientific study individually for whether by itself it reliably supports the causal claim being advocated or opposed.[235]

---

regarding the proposed mechanism); *Milward*, 639 F.3d at 18; *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prod. Liab. Litig.*, 174 F. Supp. 3d 911 (D.S.C. 2016); *In re Testosterone Replacement Therapy Prod. Liab. Litig. Coordinated Pretrial Proceedings*, No. 14 C 1748, 2017 WL 1833173, at *9 (N.D. Ill. May 8, 2017).

[233] *Ref. Man.* at 20, 21, 222, 553, 565, 591, 599 and 600.

[234] *Id.* at 19–20; *see also Milward*, 639 F.3d at 26 (reversing the district court's exclusion of expert testimony based on an assessment of the contribution of individual studies and finding that the "weight of the evidence" properly supported the expert's opinion).

[235] *Ref. Man.* at 600.

As have numerous other courts, the Third Circuit has endorsed an expert's use of the "weight of the evidence" approach to assessing the "totality" of evidence for evaluating general causation.[236] As set forth below, the PSC's experts base their general causation opinions on multiple lines of scientific evidence.

Sixth, science does not demand certainty. Nor does the law. Under Third Circuit *Daubert* standards, the trial court should not impose "a standard of scientific certainty . . . beyond that which *Daubert* envisions."[237] Plaintiffs also are not required to present evidence that is conclusive or unequivocal. "[I]n epidemiology hardly any study is ever conclusive, and we do not suggest that an expert must back his or her opinion with published studies that unequivocally support his or her conclusions."[238] Science and medicine often do not lead to certainty and the law does

[236] *See In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 858 F.3d 787, 796–797 (3d Cir. 2017) (citing *Milward*, 639 F.3d at 17 ("[t]he court treated the separate evidentiary components of [the expert's] analysis atomistically, as though his ultimate opinion was independently supported by each."); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 607 (D.N.J. 2002); *In re Tylenol (Acetaminophen) Mktg., Sales Practices, & Prod. Liab. Litig.*, 198 F. Supp. 3d 446, 458 (E.D. Pa. 2016); *In re Phenylpropanolamine (PPA) Prod. Liab. Litig.*, 289 F. Supp. 2d 1230, 1242 (W.D. Wash. 2003) (rejecting defense *Daubert* challenges which "isolate these sources [of evidence] rather than considering the whole").

[237] *Ruiz-Troche*, 161 F.3d at 86.

[238] *Knight v. Kirby Inland Marine Inc.*, 482 F.3d 347, 354 (5th Cir. 2007).

not require certainty.[239] Again, Fed. R. Evid. 702 has "a liberal policy of admissibility."[240]

B. J&J'S OMNIBUS MOTION TO EXCLUDE THE OPINIONS OF THE PSC'S GENERAL CAUSATION EXPERTS IMPROPERLY REQUESTS THAT THE COURT WEIGH THE EVIDENCE ON THE RELATIONSHIP BETWEEN TALCUM POWDER PRODUCTS AND OVARIAN CANCER

This Court has repeatedly made clear that it has bifurcated this litigation for one reason: to determine whether there is reliable evidence from which a jury could reasonably conclude that the perineal use of Talcum Powder Products can cause ovarian cancer. The question is not whether the PSC's experts or J&J's experts are correct or even what conclusion the Court would come to if it were the trier of fact. The sole question is whether each challenged expert used a reliable methodology.[241]

J&J's motion nevertheless attempts to convince the Court that it is "right" on all issues as opposed to making a serious, specific methodological challenge to the

---

[239] *Milward*, 639 F.3d at 22 (quoting *Primiano v. Cook*, 598 F.3d 558, 565 (9th Cir. 2010)).

[240] *Geiss*, 2013 WL 4675377, at *4.

[241] *See, In re Testosterone Replacement Therapy Products Liability Litigation Coordinated Pretrial Proceedings*, 2017 WL 1833173, at *9 ("At this stage, it is not the Court's role to choose between competing studies…the studies "merits and demerits…can be explored at trial.") (citation omitted); *In re Roundup Prod. Liab. Litig.*, No. 16-MD-02741-VC, 2018 WL 3368534, at *2–3 (N.D. Cal. July 10, 2018) ("So long as an opinion is premised on reliable scientific principles, it should not be excluded by the trial judge; instead the weaknesses in an unpersuasive expert opinion can be exposed at trial, through cross examination or testimony by opposing experts").

PSC's causation experts. J&J presents this Court with 120 pages of argument, not about the methodology of any expert *per se*, but covering the waterfront about how the studies and other evidence ought to be organized, interpreted and weighed and what conclusions should be drawn from the evidence. That, of course, requires the PSC to address all of these issues. Suffice it to say, there is a dispute with more recent bodies, like the IOM and Health Canada concluding that the weight of evidence supports the conclusion that perineal use of talcum powder is a likely cause of ovarian cancer, specifically epithelial ovarian cancer.

1. J&J Improperly Elevates the *Conclusions* of its Experts and Ignores that the Totality of the Evidence must be Considered

In seeking to exclude the PSC's experts and their opinions, J&J has pitted its experts' "conclusions" against the PSC's experts' "conclusions," all to support an improper argument, under *Daubert* and its progeny, that this Court should exclude the "flawed" opinions J&J does not agree with. The fact that experts reach different conclusions about a matter, however, is not a methodologic issue and is no basis for a *Daubert* challenge.

To give but one example, that is further discussed below, J&J and its experts seek to minimize the scientific reliability of the robust body of over 30 published case control studies, arguing that these studies should be ignored as they are subject

to potential "recall bias" and possible "confounding."[242] In support of its "methodologic argument," J&J liberally cites to its own experts and argues that the talcum powder cohort studies provide the *best* evidence, and that no association exists between Talcum Powder Products and ovarian cancer.[243] Again, relying on its own experts' interpretation of the cohort data, J&J adamantly argues that the PSC's experts have not been "evenhanded"[244] because they did not limit themselves to the one particular study design that J&J prefers, *i.e.*, the talc cohort studies,

The PSC's well-qualified experts have provided detailed and specific reasons for their opinions that the cohort studies alone do not tell the whole story, as J&J contends. PSC experts have explained how the body of scientific evidence *as a whole*[245] supports their conclusion that Talcum Powder Products cause ovarian

---

[242] Defs.' Mem. at 34, 36-37, 39-40.

[243] Defs.' Mem. at 48 and n. 117.

[244] Defs.' Mem. at 9, n. 16, 10-11.

[245] *See In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d at 796–797 (citing *Milward*, 639 F.3d at 17 ("[t]he court treated the separate evidentiary components of [the expert's] analysis atomistically, as though his ultimate opinion was independently supported by each."); *In re Tylenol*, 198 F. Supp. 3d at 458; *In re Phenylpropanolamine (PPA) Products Liability Litigation*, 289 F. Supp. 2d at 1242 (rejecting defense *Daubert* challenges which "isolate these sources [of evidence] rather than considering the whole"); *Alexander v. Honeywell Int'l, Inc.*, No. 1:17 CV 504, 2018 WL 4220628 (N.D. Ohio Sept. 5, 2018); *In re Seroquel Products Liability Litigation*, 2009 WL 3806435; *McMunn v. Babcock & Wilcox Power Generation Grp., Inc.*, No. 2:10CV143, 2014 WL 814878 (W.D. Pa. Feb. 27, 2014); *In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d 1291 (N.D. Fla. 2018).

cancer, *including the positive evidence from the cohort studies*. In this regard, the PSC's experts have testified that the cohort studies do show an increased risk of ovarian cancer and a statistically significant risk of serous invasive ovarian cancer.

As scientists outside this litigation have noted, the cohort studies that J&J relies on so heavily to trump every other piece of observational data in this case - Gertig (2000); Gates (2010); Houghton (2014) and Gonzalez (2016) - were subject to serious "misclassification" biases and were not powered or designed to address the association between talcum powder and ovarian cancer, a rare disease.[246] There

[246] *See* Reports and deposition testimony of the PSC's experts thoroughly outlining the flaws with cohort studies: McTiernan Rep. at 19, 46-48, 64 ("While the cohort studies on average showed more attenuated relative risks of ovarian cancer in relation to use of talcum powder product use, these studies were not well designed to determine true risk for ovarian cancer and perineal talc use."); McTiernan Dep. at 126:6-127:22, 219:19-222:12; Siemiatycki Rep. at 15-16, 48, 56 ("The women in the cohort studies were "locked into" their exposure category at baseline of the cohort study. If there were women who in fact started using powders after the baseline, they would be incorrectly labelled as non-users. And, if there were indeed a risk associated with use of talc powders, the risk estimate would be diluted by the incorrect inclusion of users among non-users."); Moorman Rep. at 8, 25; Moorman Dep. at 199:18-200:9; Singh Rep. at 10-11, 47 ("…evaluating the association between talc use and ovarian cancer was not the a-priori primary objective of the study but evaluated as a subsequent hypothesis, with its inherent limitations"); Singh Dep. at 155:20-156:6. Kane Rep. at 24 (It is well understood that cohort studies are particularly ill suited to study rare diseases with long latencies); McTiernan Rep. at 46-48 ("The sample sizes (numbers of cases) of most of the cohort study publications were likely too small to be able to detect a relative risk in the order of 1.24 (the value found in the Terry pooled analysis) with reasonable power, especially for different histologic subtypes."); Moorman Rep. at 27 ("As the authors [of the Sister Study] acknowledged in their paper, if latency (the time between exposure and diagnosis of

were serious limitations to these cohort study analyses, which arguably could have attenuated the relative risks of ovarian cancer. Notably, none of the studies were specifically designed to investigate the relationship of talcum powder use and risk of ovarian cancer. Rather, they were designed to study a large number of outcomes and a wide variety of exposures. As such, the PSC's experts concluded that the case-control studies and meta-analyses—*along with evidence gathered from the cohort studies*—provide the best observational evidence in favor of the association between ovarian cancer and Talcum Powder Products.[247]

Under analogous circumstances, courts have held that disputes between experts about how to weigh different studies and different study designs is precisely the type of question that should be resolved by a jury. For example, in *In re Testosterone*, the defendant, AbbVie, made the identical arguments that J&J makes here. AbbVie claimed that the plaintiffs' general causation experts should be excluded because they did not weigh the relevant epidemiology in the same way that AbbVie's experts had. The court in *In re Testosterone* determined that this was not a *Daubert* issue at all:

---

cancer) is 15 to 20 years, the exposure assessments do not accurately reflect the period of risk.").

[247] McTiernan Rep. at 48; Siemiatycki Rep. at 48 ("On balance, I believe the results of each of these case-control studies concerning female use of powders and ovarian cancer are credible, and perhaps more so (for reasons given in section 7.2), than the analogous results of each of these cohort studies").

> According to AbbVie, plaintiffs' experts rely on only a few facially favorable studies, while ignoring (1) those studies' flaws, (2) the fact that the studies are inconsistent with one another, and (3) the studies' authors' own unwillingness to conclude that they demonstrate a causal association. As discussed above, a review of plaintiffs' experts' reports reveals that they carefully addressed the merits, flaws, and implications of both favorable and unfavorable studies. [Defendant] is likely correct that no single piece of evidence the experts rely upon is sufficient to support their causation opinions. But the experts have adequately explained why they have reached their conclusions on the basis of the evidence as a whole. *See Milward*, 639 F.3d at 23. The Court's inquiry at this stage is to determine whether the experts "considered sufficient data to employ the methodology," not whether their consideration of the data led to the correct conclusion. *Stollings v. Ryobi Techs., Inc.*, 725 F.3d 753, 766 (7th Cir. 2013). *For an expert conclusion that is subject to doubt, "[i]t is the role of the jury to weigh these sources of doubt."* [248]

Citing to the law in both the Second and Third Circuits, the court in *In Testosterone* made clear that, so long as the experts carefully explored the data, discrepancies should be left for cross-examination:

> Ultimately, experts on both sides of this litigation have analyzed the existing epidemiological evidence in detail, criticizing the studies on which the other side relies, and drawing different conclusions from the literature. This is not a case in which plaintiffs' experts have simply cherry-picked the favorable studies while ignoring unfavorable studies entirely. *Cf. In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 449, 460–61 (E.D. Pa. 2014) (excluding expert who failed to provide an adequate rationale for excluding her own, unfavorable peer-reviewed studies from her expert report); *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d 398, 425–26 (S.D.N.Y. 2005) (excluding experts whose reports failed to even mention highly relevant, but unfavorable, studies). At this stage, it is not the Court's role to choose between competing studies. *Schultz v. Akzo Nobel Paints,*

[248] *In re Testosterone*, 2017 WL 1833173, at *9.

> *LLC*, 721 F.3d 426, 433 (7th Cir. 2013). The studies' "merits and demerits . . . can be explored at trial."[249]

Additionally, the court in *In re Roundup* rejected a similar *Daubert* attack made by defendant Monsanto challenging the plaintiffs' experts. In *Roundup*, the general causation question was whether glyophosate, a commonly used herbicide, can cause Non-Hodgkins Lymphoma (NHL).[250] Monsanto attacked the plaintiffs' experts in the same way that J&J does here, calling their opinions of the existing epidemiology a methodologic flaw which must be excluded. The *Roundup* court rejected this attack even where the evidence appeared tilted towards Monsanto:

> .... But the Court concludes that the opinions of these experts, while shaky, are admissible. They have surveyed the significant body of epidemiological literature relevant to this question; identified at least a few statistically significant elevated odds ratios from case-control studies and meta-analyses; identified what they deem to be a pattern of odds ratios above 1.0 from the case-control studies, even if not all are statistically significant; emphasized that studies of glyphosate have focused on many different types of cancer but found a link only between glyphosate and NHL; given legitimate reasons to question the results of the primary study on which Monsanto relies; and concluded, in light of all the available evidence, that a causal interpretation is appropriate [251]

Yet another example of a court rejecting many of the same attacks lodged here by J&J against the PSC's experts is Judge Pisano's decision in *In re Fosamax*

---

[249] *Id.*

[250] *In re Roundup*, 2018 WL 3368534, at *1.

[251] *Id.* at *36.

(Alendronate Sodium) Prod. Liab. Litig., No. CIV.A. 08-08, 2013 WL 1558690 (D.N.J. Apr. 10, 2013) (Pisano). In *In re Fosamax*, defendant Merck criticized the plaintiffs' experts, stating that they did not explain the scientific methodology used or how it was reliable;[252] just listed some studies only, some of which support causation;[253] and, did not evaluate studies for possible biases and confounders was similarly an issue for cross-examination.[254] Even in that circumstance (not present here), Judge Pisano concluded that Merck's criticisms went to the weight, not admissibility of the experts' testimony, and that "Defendant is free to address these issues on cross-examination."[255]

2. Causal Assessments Require the Exercise of Professional Judgments upon which Experts can Reach Different Conclusions

J&J argues that because there are differences of opinion amongst experts, it has made a proper methodology challenge against the PSC's experts. J&J repeatedly urges the Court to take notice of what it calls "fundamental epidemiologic principles" to support its arguments.[256] However, J&J's "fundamental" concept involves a mechanical application of limited scientific information to reach a

[252] *Id.*

[253] *Id.*

[254] *Id.*

[255] *Id.* at *4.

[256] Defs.' Mem. at 9-14.

conclusion, whereas general causation is not a scientific concept that is evaluated through overly-simplistic and mechanical rules. The *Reference Manual* notes that the question of causal inference is not subject to a mathematical or mechanical formula and a difference in opinion is simply not the basis to exclude a qualified experts' opinion. [257]

As stated above, a causal inference requires an examination of the *totality of the scientific evidence*. When an issue involves a multitude of evidence, appropriate scientific methodology requires consideration of the cumulative effect of all of the scientific evidence and not only certain parts. "Scientific inference typically requires consideration of numerous findings, which, when considered alone, may not individually prove the contention."[258] This is how science outside of the courtroom functions. There is simply no definitive checklist or magic formula for making scientific judgments.

As Leon Gordis, MD, an editor of the *Reference Manual* observed in his textbook *Epidemiology* (5th Ed):

> Although it may be a desirable goal to place causal inferences on a firm quantitative and structural foundation, at present we do not have all of the information needed for doing so. [The Bradford Hill aspects] should therefore be considered to be only guidelines that can one of most value

[257] *Ref. Man.* at 600 (rejecting an "algorithmic methodology" to determine causation).

[258] *Ref. Man.* at 19–20.

> when coupled with reasoned judgment about the entire body of available evidence, in making decisions about causation.[259]

That is not only true for epidemiology generally, but also cancer epidemiology. Reasoned judgment and difference of opinion are part of the process. In his Cancer Epidemiology textbook entitled *Risk Factors for Cancer In the Workplace*, the PSC's expert, Jack Siemiatycki, Ph.D, bluntly observed the simple truth: "Equally competent scientists, examining the same information, can arrive at different [causal] conclusions."[260]

J&J's motion does not describe either a true *methodologic* challenge or a legitimate contention that the PSC's experts *refused* to consider relevant evidence (*e.g. In Re Zoloft)*. That the PSC's experts' opinions may be different than those of J&J's experts, simply presents a jury question.

3. J&J's Citation to its own Causation Experts Illustrates that General Causation is Properly Resolved by a Jury

Read carefully, J&J's motion does not focus on what the PSC's experts did (or did not do) in relation to any objective standard but, instead, attacks how the PSC's causation experts approached the data as compared Defendants' experts. J&J's attempt to persuade the Court by citing the opinions of its own experts is improper. J&J's argument simply highlights that its *Daubert* challenge is not about

[259] Leon Gordis, *Epidemiology* at 260. (5th ed. 2013), attached as **Exhibit 133**.

[260] *Id.* at 298.

methodology, but about winning a proverbial "battle of the experts." Of course, such battles are for the jury to decide.

To illustrate, five of J&J's experts (Drs. Ballman, Merlo, Diette, Saenz and Holcomb) are cumulatively cited in J&J's motion approximately 100 times. Defendants' experts "explained," "noted" or "testified" about various unsupported propositions approximately 20 times.[261] Several of J&J's experts (like Drs. Diette, Merlo, and Holcomb) are cited almost as often, if not more often, than some of the PSC's experts being challenged.

J&J seems to believe that by endlessly asserting the opinions of their experts, the sheer volume will convert its dispute over the PSC's experts' conclusions into a methodological challenge. But the real question is whether there is *any* evidence that the PSC's experts engaged in unreliable methodologies in reaching their opinions. As set forth below, there is none.

4. Health Canada's December 2018 Independent Analysis of the Talcum Powder Ovarian Cancer Causation Question Corroborates that the Methodology Used by the PSC's Experts is Proper

In arguing that the PSC's general causation experts lack a sufficient basis for their conclusions, J&J strenuously argues that others (like FDA, NCI and IARC) reviewed at least some data on the talcum powder-ovarian issue years ago and found

[261] Defs.' Mem. at 56.

"insufficient" evidence to support a firm casual association between Talcum Powder Products and ovarian cancer.[262] They call this a "consensus" and repeatedly argue that it should control the resolution of this motion.

Specifically, J&J highlights a 2006 IARC Assessment (which, in fact, found both association and consistency, and said that causation was possible) and a 2014 letter from an FDA employee (which, in fact, found association and biologic plausibility for talc migration) to support it argument that there is no scientific dispute and that the issues are well settled. According to J&J, these "findings" alone "prove" that the PSC's experts produced "science for the courtroom, not ... the laboratory."[263] Assuming J&J correctly cited these materials, which they did not, these are dated evaluations that a jury should consider within the proper context of new and relevant evidence.[264]

---

[262] Defs.' Mem. at 7.

[263] Defs.' Mem. at 3.

[264] Even if these agencies had considered all of the evidence (which they did not), and even if they had done an up-to-date and complete causal assessment of all the data (which neither ever claimed to have done), that would still not be dispositive... In *In Re Testosterone*, Defendant made the exact same argument except, unlike here, the FDA had in fact looked at every study that plaintiff's experts had relied on and it reached an opposite conclusion than plaintiffs' experts did. Even then, FDA's action was not dispositive under *Daubert*:

> AbbVie emphasizes that the FDA reviewed the same data, specifically the same epidemiological studies, as plaintiffs' experts but reached a different conclusion about whether TRT is associated with cardiovascular injuries. AbbVie, however, has not cited any authority for the proposition that conclusions the FDA makes in its review of

These older evaluations notwithstanding, J&J conspicuously ignores the recent December 2018 causal assessment by Health Canada.[265] Health Canada is not only the most recent government body to consider the issue, it is the *only* governmental body to have demonstrably performed a Bradford Hill analysis on the talcum powder-ovarian cancer question. Indeed, it was published after plaintiffs' expert reports were disclosed in November 2018. The similarity of the causal assessment performed by Health Canada to the casual assessment performed by the PSC's causation experts is striking. Health Canada not only employed precisely the *same* methodology, but it reached the following conclusion—a conclusion that Health Canada reiterates no less than 3 times in the report:

> The most recent meta-analysis detailed above (Taher *et al.* 2018), and consistent with the Hill criteria, suggests a small but consistent statistically significant positive association between ovarian cancer and perineal exposure to talc. ***Further, available data are indicative of a causal effect***.[266]

> available data are legally or scientifically dispositive on the issue of causation. *In this context, the FDA's opinion is analogous to the opinion of any other expert in this case. Thus, although the FDA may have a different interpretation of the studies relied upon by plaintiffs' experts, "it is left to the trier of fact, not the reviewing court, to decide how to weigh the competing expert testimony.*

In re Testosterone, 2017 WL 1833173, at *13 (emphasis added).

[265] *See generally* Health Canada Assessment.

[266] *Id.* at 21 (Emphasis added); *see also id.* at iii ("available data are indicative of a causal effect."); *id.* at 28 (same).

The Health Canada report demonstrates, and independently corroborates, objectively that: a) the methodology the PSC's experts used to address the general causation question is the exact same methodology used outside the Courtroom; b) the epidemiologic evidence used by the PSC's experts is exactly the same as the evidence used outside the Courtroom, and; c) the methodology used by PSC's experts could reasonably lead to a finding of causation.[267]

Health Canada scientifically and systematically reviewed the available epidemiologic and non-epidemiologic evidence relating to talc and human disease using the Bradford Hill criteria, as did the PSC's experts.[268] With respect to ovarian cancer specifically, that scientific analysis entitled "*Perineal Exposure to Talc*" concludes with the unambiguous statement that the available epidemiologic and non-epidemiologic evidence "as indicative of a casual effect."[269]

[267] Since its issuance, J&J has lobbied Heath Canada to change its assessment, submitting multiple large briefing booklets and culminating in a private meeting on April 24, 2019. On the outside chance that J&J's intensive lobbying efforts results in Health Canada reversing course on its ultimate causation conclusion, that would make no difference to the importance of this current assessment. The issue before the Court is methodology, not conclusions. Health Canada's methodology on this topic (regardless of its conclusion) independently corroborates the methodology employed by the PSC's experts.

[268] McTiernan Dep. at 307:18-309:24 (Health Canada performed a full causal analysis with a methodology similar to that set forth in her own report).

[269] Health Canada Assessment at 21.

Faced with the unambiguous scientific analysis and scientific conclusion, J&J tries to conflate its regulatory standard for taking precautions (like issuing warnings), under Canadian law, with its scientific conclusion about cause-and-effect. For instance, J&J focuses on whether that scientific evidence, once assessed, met the low threshold for regulatory action which is defined under Canadian law. In its motion, J&J ignores the scientific finding and highlights the regulatory one.[270] In footnote 14 of its memorandum J&J selectively (and misleadingly) quotes half the sentence relating to the Health Canada regulatory finding, the whole sentence containing both its scientific and regulatory finding reads as follows:

> The meta-analyses of the available human studies in the peer-reviewed literature indicate a *consistent and statistically significant positive association between perineal exposure to talc and ovarian cance*r. ***Further, available data are indicative of a causal effect***. Given that there is potential for perineal exposure to talc from the use of various self-care products (*e.g.*, body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs), a potential concern for human health has been identified.[271]

As important as it may be that Health Canada made causal findings, the existence of causal findings is almost beside the point for the purposes of J&J's *Daubert* challenge. What is most important is the Bradford-Hill methodology

[270] Defs.' Mem. at 9, n.16 and 11.

[271] Health Canada Assessment at iii, 29.

employed by Health Canada.[272] Health Canada's analysis looked at the same studies as the PSC's experts, including the relative strengths of the case-control and cohort studies, and at issues such as bias and confounding.

Health Canada did not blindly apply a "hierarchy of evidence" and did not elevate the cohort studies that J&J (wrongly) asserts are "more reliable."[273] In fact, it did what the PSC's expert did—weigh the strengths and weaknesses of each ovarian cancer study. Rather than declaring that the cohort studies negated the case-control studies, Health Canada (like the PSC's experts) concluded that the cohort studies actually were consistent with the case-control studies and that any differences between them were likely due to the *short-comings of the cohort studies* and not any short-comings of the case-control studies. According to Health Canada:

> The individual cohort studies did not show a statistically significant association between perineal talc use and ovarian cancer (Berge *et al.* 2018; Penninkilampi and Eslick 2018; Taher *et al.* 2018). *However, there was a positive association, with statistical significance, specific to invasive serous-type ovarian cancer in the cohort studies (OR = 1.25) (Penninkilampi and Eslick 2018).* Given the long latency for ovarian cancer, the follow-up periods may not have been sufficient to capture all the cases for the individual cohort studies. Also, given the rarity of ovarian cancer, many of the available human studies may not be sufficiently powered to detect a low OR. Sample sizes were not large enough to detect a 20 to 30 % increase in risk; a group of over 200,000 women

[272] *Id.* at 15.

[273] Defs.' Mem. at 61-63, 64 n. 155.

> would need to be followed for over 10 years in order to detect a 20% (above background) increased risk with statistical significance (Narod 2016). With larger sample sizes, more individual studies may have demonstrated stronger associations.[274]

Thus, Health Canada assessed the totality of the epidemiologic and biologic evidence, according to the Hill framework, and came to conclusions consistent with the opinions reached by the PSC's experts:

- For "STRENGTH" it found association between 1.2 and 2.0;
- For "CONSISTENCY," it found a "consistent and significantly significant increased risk for ovarian cancer with perineal use;"
- For "SPECIFICITY" it found that "perineal talc is associated with cancer of the ovary and no other organs;"
- For "TEMPORALITY" it found that all cases of talc exposure "preceded the reported outcome;"
- For "BIOLOGIC GRADIENT" it found that there was limited data but noted that there was "some evidence of increased risk of ovarian cancer with increasing perineal applications of talc," even though not statistically significant; and,
- For "BIOLOGIC PLAUSABILITY" it found that there is evidence of retrograde transport that supports the biologic plausibility of the association between talc application and ovarian exposure. [NOTABLY, Health Canada assumed that there was no asbestos].[275]

[274] Health Canada Assessment at 20.

[275] *Id.* at 1, 21-22 (assumed no asbestos).

Objectively, the Health Canada Assessment provides independent *indicia of reliability* to PSC's experts' causation methodology.[276] For that reason, J&J's motion should be denied.

C. THE PSC'S CAUSATION EXPERTS MAY RELIABLY OPINE THAT THE CONSISTENCY OF ASSOCIATION ASPECT OF BRADFORD HILL'S CAUSATION GUIDELINES IS SATISFIED

1. There is Scientific and Medical Consensus that the Observational Studies of Talcum Powder and Ovarian Cancer Show a Consistent Association

The question of whether the perineal use of talcum powder is associated with ovarian cancer has been the subject of epidemiologic interest and study over the past forty years. It has been studied by different researchers in different countries using different study designs, including case-control studies, cohort studies, pooled analyses and meta-analyses. The vast majority of these studies, regardless of study

[276] In contrast to J&J's treatment of the recent and full Bradford Hill evaluation of Health Canada, J&J highlights the Musser Letter denying a Citizens' Petition for Talc for the proposition that the "FDA has concluded that existing science does not support the conclusion that talc is a cause of ovation cancer." *First,* Dr. Musser did not perform a Bradford Hill analysis as Health Canada and the PSC's experts did. *Second*, the analysis is from a 5-year old letter that does not incorporate the recent studies and meta-analyses that Health Canada and the PSC's expert did. *Third*, unlike the Canadian Assessment that was performed *without* J&J influence and lobbying, J&J met and lobbied FDA *ex parte* to deny the Citizens Petition. *See* Deposition of Linda Loretz, October 1, 2018 at 490:4-506:22, attached as **Exhibit 134**; *see also* May 8, 2009 FDA Meeting Minutes, attached as **Exhibit 135**. *Fourth*, J&J did not inform FDA that its internal testing of talc had revealed the presence of asbestos, though FDA had clearly asked about it. *Id.*

design, have shown a positive association between talcum powder use and ovarian cancer, and most of these studies have statistically significant results.

The association between talcum powder exposure and ovarian cancer—and its implications for a causal conclusion--has become so obvious in recent years that its denial has been called scientifically disingenuous. For example, in a 2016 article entitled *Talc and Ovarian Cancer*, it was observed that:

> It is unlikely that the association between talc and ovarian cancer is due to confounding so it is fair to say that if there is a statistically robust relationship between talc and ovarian cancer, it is likely to be causal (albeit with intermediate factors such as inflammation). In any case, given the number of hazard ratios reported in the literature between 1.1 and 1.4 in both case control and cohort studies, **it is disingenuous to state that there is no evidence that talc is associated with ovarian cancer.**[277]

The observations about the association and consistency of association have been noted by numerous researchers and commentators who have stated, for example, that "perineal talc use is associated with a 24%-39% increased risk of ovarian cancer" and the "confirmation of an association in cohort studies between

[277] S.A. Narod, *Talc and Ovarian Cancer*, 141 Gynecologic Oncology 410, 411 (2016) (emphasis added), attached as **Exhibit 136**. *See also*, Pennikilampi (2018) at 41 ("In general, there is a consistent association between perineal talc use and ovarian cancer.").

perineal talc use and serious invasive ovarian cancer is suggestive of a causal relationship**."**[278]

The conclusion that there is an association between talcum powder and ovarian cancer—and the overall consistency of that association—is not simply reflected in the writings of a few random commentators--or the PSC's experts. Health Canada noted that the entire body of epidemiologic evidence to date was "indicative of a causal effect."[279] In 2016, the United States National Academy of Science, Institute of Medicine (IOM) concluded that "the use of perineal talcum powder has been associated with a 20 to 30 percent increased risk of ovarian cancer, although it has also been shown to vary by histological subtype."[280] Additionally, although the FDA has not yet taken regulatory action on Talc, the 2014 FDA Musser letter denying a "*Citizen's Petition*" agreed that "the best evidence for an association or causal relationship between genital talc exposure and ovarian cancer comes from

---

[278] *Id*.; *see also* Wu (2009) (…"[M]ost of the 20 epidemiologic studies on talc and ovarian cancer show a consistent 30-60% increased risk associated with Talc use."); Terry (2013) ("In summary, genital powder is a modifiable exposure associated with a small to moderate increased risk for most histological subtypes of epithelial ovarian cancer"); Cook, *et al.* . (1997) ("These results offer support for the hypothesis, raised by prior epidemiologic studies, that powder exposure from perineal dusting contributes to the development of ovarian cancer."); Cramer (1999) ("In summary, we have demonstrated a consistent association between talc and ovarian cancer that appears unlikely to be explained by recall of confounding.").

[279] Health Canada Assessment at iii, 21. J&J is simply mischaracterizing the scientific conclusions reached in that document.

[280] *See infra* n 169.

epidemiologic data *which shows a statistically significant but modest increased risk of epithelial ovarian cancer, especially with serous histology, among women with a history of genital dusting with talcum powder*."[281]

Lastly, the consistent association is reflected in gynecologic textbooks.[282]

2. J&J's Challenge to the Methodology for Assessing Association and Consistency of Association Depends Solely on an Improper Two-Step Algorithm of "Significance Testing" and "Hierarchy of Evidence" Sorting

J&J's real argument is not that the PSC's experts' methodology is flawed but that they did not adhere to the two-step methodology that J&J's experts employed in reaching their opinions.[283] J&J falsely claims that there is a methodological flaw in the PSC's experts' approach.

As described in the *PSC's Motion to Exclude J&J's Epidemiology Experts*, J&J's experts' two-step methodology erroneously involves a combination of two alleged methodologic "principles" broadly described on pages 9-16 of J&J's Memorandum as "Fundamental Epidemiologic Principles" under the headings "Hierarchy of Evidence" and "Relative Risks and Odds Ratios." Tellingly, and as

[281] Musser Letter at 5.

[282] Eeles, et al. (2018) at 337.

[283] The two-step approach is loosely but incompletely described in J&J's memorandum under the guise of "fundamental epidemiologic principles" on pages 9-14 and it is inappropriately applied to the talc and ovarian cancer question on pages 14-22.

set forth in the *PSC's Motion to Exclude J&J's Epidemiology Experts*, J&J's experts have failed to cite any real support justifying their interpretation of such a flawed two-step methodology.[284] This two-step methodology is:

First, J&J and its experts assert that it is generally accepted that epidemiologists perform "statistical significance testing" (hereinafter "significance testing") on all observational studies to determine both proof of association *and* consistency of association. Significance testing maintains that observational studies that show a positive association that are not statistically significant are—*by virtue of their non-significance alone and without reference to either the reported association or the reported confidence interval*--inconsistent with studies that show a positive association that are statistically significant. Citing only its expert, Dr. Ballman, J&J argues that a result that is not significant to a p-value less than .05 means, by definition, that ***"there is no association between exposure and outcome."***[285] According to J&J the PSC's experts committed a methodologic error by not using "significance testing" as the metric to measure association and consistency.[286]

Second, and to compound the error, J&J asserts that there is a "generally accepted" and "long standing, well-established principle in the epidemiologic

[284] *PSC's Motion to Exclude Epidemiology Experts* at 7-44.

[285] Defs.' Mem. at 14 (emphasis added).

[286] *Id.* at 61-66.

community" that there is a "hierarchy" of evidence based on generic study design.[287] Under that design, cohort studies are stronger evidence than case control studies by simple virtue of their design.

As set forth in the *PSC's Motion to Exclude J&J's Epidemiology Experts*, it is J&J's causation experts' opinions that should be excluded, not the PSC's. At most, however, all that J&J is raising is a dispute about the PSC's experts' conclusions and not the reliability of their methodology.

a. The PSC's causation experts properly assessed all statistical data about the talcum-ovarian cancer association and properly did not perform "significance testing"

J&J begins by criticizing the PSC's experts for allegedly failing to "significance test," *i.e.* to sort the talc observational studies according to statistical significance alone. According to J&J, the PSC's experts erred methodologically by failing to perform a mechanical multiple-choice "significance--yes" and "significance--no" exercise—also called "significance testing" in the epidemiologic literature. This is a "fundamental" epidemiologic error according to J&J, requiring exclusion.[288]

[287] *Id.* at 9-12.

[288] *Id.* at 5, 9-14, 47-67.

According to J&J, the fact that some studies show statistical significance while others do not "by itself, compels the conclusion that the data are inconsistent."[289] J&J's contention, that the PSC's experts should have "significance tested" the data and found that non-significant results are "inconsistent" with statistically significant ones, is flawed. A non-significant result does not mean, as J&J and Dr. Ballman categorically state, that the study concludes that "there is no association between exposure and outcome." This premise, the central error of "significance testing", is itself an unsound methodology and its strict application as the sole metric for association has been roundly rejected by both the epidemiologic and statistical communities.[290]

The Third Circuit was one of the first Circuits to express concern with significance testing,[291] a concern that made its way into the *Reference Manual*. Regarding significance testing, the 2011 edition of the *Reference Manual* stated that:

---

[289] Defs.' Mem. at 5.

[290] *Modern Epidemiology* at 25; Borenstein (2009), at 251; Rothman (2014) at 1060; Ronald L. Wasserstein, *et al., Moving to a World Beyond "p<.05"*, 73 The American Statistician 1 (Supp. 1 2019), attached as **Exhibit 137**; Amrhein, Greenland, & McShane, *Retire Statistical Significance*, 567 Nature 305 (2019), attached as **Exhibit 138**.

[291] *See In re TMI Litig. Cases Consol. II, In re*, 922 F. Supp. 997, 1017 (M.D. Pa. 1996) ("The court is in agreement with Plaintiffs that there is presently an ongoing dialogue within the relevant scientific community on the issue of significance testing. Moreover, the court is aware that the debate has carried over into the judicial arena."(citations omitted)); *see also Kadas v. MCI Systemhouse Corp.*, 255 F.3d 359, 362 (7th Cir. 2001) ("The 5 percent test is arbitrary; it is influenced by the fact that

> Epidemiologists have become increasingly sophisticated in addressing the issue of random error and examining the data from a study to ascertain what information they may provide about [a relationship] *without the necessity of rejecting all studies that are not statically significant.*[292]

Importantly, courts have continued to be skeptical of rigid statistical testing.[293]

As demonstrated below, however, the concept of "significance testing" is no longer just "unsophisticated," it is a fundamental error that is now specifically rejected by the epidemiologic and statistical communities who have demonstrably and publicly rebuked it.

---

scholarly publishers have limited space and don't want to clog up their journals and books with statistical findings that have a substantial probability of being a product of chance rather than of some interesting underlying relation between the variables of concern.").

[292] *Ref. Man.* at 578-9.

[293] *See, e.g., In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d at 793 (while statistical significance is a useful metric for a causal association, it is not the sole or exclusive metric); *see also In re Roundup Products Liability Litigation*, 2018 WL 3368534, at *2–3; *In re Testosterone* 2017 WL 1833173, at *10 (citing *Ref. Man.* at 378-9); *Daubert*, 509 U.S. 579 ("The fact that a scientific community may require a particular level of assurance for its own purposes before it will regard a null hypothesis as disproven does not necessarily mean that expert opinion with somewhat less assurance is not sufficiently reliable to be helpful in the context of civil litigation." (footnote omitted)).

i. The PSC's experts' methodology included an analysis of all of the statistical data in the observational studies, not just statistically significant data

Before addressing the statistical and epidemiologic communities' rebuke of "significance testing," however, it is important to state that notwithstanding J&J's argument, neither the PSC nor its experts "attack the long-established concept of statistical significance."[294] Nor do the PSC's experts "disregard" statistical significance. The PSC and its experts fully agree with the *Zoloft* court that although there may be a casual association *in the absence* of any statistically significant studies in some instances, statistical significance remains a useful metric for determining whether the results of a given study likely shows a real association.[295]

Therefore, and fundamentally, the PSC and its experts do not "attack" statistical significance. Nor would it be in its best interests to do so – since the majority of studies show a statically significant increase risk between the genital use of talcum powder and epithelial ovarian cancer. What the PSC attacks, is the *misuse* and *misapplication* of statistical significance in the form of "significance testing" to created inconsistency where none exists. In other words, the PSC and its experts do

[294] Defs.' Mem. at 5.

[295] *In re Zoloft*, 858 F 3d at 793; *see also*, *In re Roundup*, 2018 WL 3368534 at * 8 (citing *In re Zoloft*); compare with *In re Tylenol,* 2016 WL 4039286, at *2 (finding causation in the absence of statistically significant observational or clinical trial data).

not convert statistical significance from the "useful" metric that the *Zoloft* and *Roundup* courts described into the mechanical "yes" and "no" *litmus* test for association that J&J advances. To do so would ignore other useful metrics of association like "risk estimates" and "confidence intervals" which J&J's pretends to discuss, but does not. As set forth below, and as described in *PSC's Motion to Exclude J&J's Epidemiology Experts*, significance testing without reference to any other useful metric of association, *e.g.* non-significant but positive risk ratios and confidence intervals that overlap the risks seen in statistically significant studies, is an unreliable fallacy well-recognized in the epidemiologic and statistic community.

Indeed, the PSC's experts (and independent entities like Health Canada, for example) relied *heavily* on the statistically significant evidence to conclude that Talcum Powder Products are associated with ovarian cancer. These include the following facts:

- Over half of the studies that looked into the question showed statistically significant results between 1.1-1.7;[296]
- The 8 published meta-analysis of studies and several unpublished ones, which are designed to increase the

[296] McTiernan Rep. at 9, 41; Siemiatycki Rep. at 72-74; Moorman Rep. at 13; Singh Rep. at 17, 28-47, 62-63; Kane Rep. at 16-23; Carson Report at 9; Clarke-Pearson Report at 6-8; Smith-Bindman Report at 28-30; Smith Report at pgs. 8-16; Wolf Report at 5-8.

power of any one study to detect an effect, showed a statistically significant risk between 1.25-1-45;[297] and,

- The Penninkilampi (2018) meta-analysis of **cohort** studies (the kinds that J&J believes are most reliable), demonstrated a statistically significant increased risk of serous invasive ovarian cancer.[298]

[297] McTiernan Rep. at 48-56; 56 ("The summary relative risks were quite consistent across the meta-analyses and the pooled analysis, ranging from 1.22 to 1.4 for any versus no use of perineal talcum powder products."); Moorman Rep. at 12 ("meta-analyses of genital talc exposure and ovarian cancer calculated summary relative risks that were very consistent across the publications, ranging from 1.22 to 1.36, all with 95% confidence intervals excluding 1, indicating that women who reported talc use were at statistically significant increased risk for ovarian cancer. Similarly, the pooled analysis of eight case-control studies reported an overall odds ratio of 1.24 (95% confidence interval (CI) 1.15-1.33)."); Moorman Dep. at 313:10-16 ("I think that the meta-analyses show consistent conclusions of a 25 to 30 percent increased risk for ovarian cancer; and that coupled with the other criteria that I considered -- the biological plausibility and the various other Bradford Hill criteria -- that I came to the conclusion that talc is a cause of ovarian cancer."); Singh Rep. at 20-27, 53; Kane Rep. at 26-29, 33; Deposition of Sarah Kane, MD, Jan. 25, 2019 ("Kane Dep.") at 351:8-12, see attached as **Exhibit 139**.

[298] Moorman Rep. at 18 ("…the recent meta-analysis by Penninkilampi and Eslick reported a statistically significant association with the invasive serous subtype of ovarian cancer, which is both the most common subtype and the one with the worst prognosis") (citing Penninkilampi (2018)); Moorman Dep. at 186:10-187-8; Carson Rep. at 6; Clarke-Pearson Rep. at 8 ("the use of talcum powder statistically increases a woman's risk of developing EOC by approximately 30 percent (Odds ratio 1.31; Penninkilampi 2018). Every meta-analysis before 2018 also reported similar increase in the risk of developing EOC with the use of talcum powder."); Smith-Bindman Rep. at 22 ("the cohort studies showed an increased risk of serous invasive cancer subtypes for perineal talc use compared to no use (OR=1.25)"); Smith Rep. at 14; Wolf Rep. at 8.

What the PSC's experts did not do, and what J&J and its experts argue they should have done, is "significance test" the data. In other words, J&J believes that the PSC's experts should have asked the seemingly innocuous question: "Are the results statistically significant?" and sort them with a simple "yes" or "no." J&J contends that the "yes" or "no" answers are conclusively meaningful. But they are not, and the PSC's experts know that. This is the reason the PSC's experts did much more than simply do a mechanical exercise of sorting studies into yes and no categories. The PSC's experts looked at what the data actually described. They analyzed and assessed whether the non-significant risk estimate was positive for an association and assessed the confidence intervals to see if they included the statistically significant results seen in the case-control studies.[299] Indeed, the *Reference Manual* describes confidence intervals to be "more valuable than

[299] McTiernan Rep. at 41-42 ("Among the 8 studies which were not statistically significant, 7 had a sample size lower than that estimated to be needed to have power to detect a statistically significant result. It is important to note that while the 8 studies did not have statistically significant results, they provide relevant data because their relative risk estimates were consistent with the 16 studies that showed statistically significant results."); Siemiatycki Rep. at 49, 64; Moorman Rep. at 29; Kane Rep. at 23-25; Carson Rep. at 9 ("three cohort studies did not find a significant relative risk of perineal talcum powder exposure leading to ovarian cancer, but did show positive nonsignificant trends."); *see also* Carson Dep. at 244:19-245:21 ("the vast majority of all of the studies show a positive odds ratio or relative risk, even if they don't rise to the level of significance."); Smith-Bindman Rep. at 18-30; Smith Rep. at 8-16; Wolf Rep. at 5-8.

[statistical tests]"[300] and the Third Circuit agrees.[301] With respect to the talcum-ovarian cancer data specifically, the PSC's experts noted that:

- The non-significant risk ratios for the remaining studies, including the Cohort studies, were positive; and
- The confidence intervals reported for the remaining non-significant studies, including the Cohort Studies overlapped 1.2-1.25 meaning that the true risk seen in these studies could have been as high as 20-25% to a 95% certainty thereby being consistent with both the statistically significant studies and the meta analyses.[302]

[300] *Ref. Man.* at 253. Confidence Intervals are defined as "An estimate, expressed as a range, for a parameter. For estimates such as averages or rates computed from large samples, a 95% confidence interval is the range from about two standard errors below to two standard errors above the estimate. Intervals obtained this way cover the true value about 95% of the time, and 95% is the confidence level or the confidence coefficient."

[301] The Third Circuit described confidence intervals (i.e., the range of values that would be found in similar studies due to chance, with a specified level of confidence) and their use as an alternative to statistical significance in *DeLuca by DeLuca v. Merrell Dow Pharm., Inc.*, 911 F.2d 941, 948–49 (3d Cir. 1990). *See also Milward*, 639 F.3d at 24–25 (recognizing the difficulty of obtaining statistically significant results when the disease under investigation occurs rarely and concluding that district court erred in imposing a statistical significance threshold).

[302] McTiernan Rep. at 41-42 ("Among the 8 studies which were not statistically significant, 7 had a sample size lower than that estimated to be needed to have power to detect a statistically significant result. It is important to note that while the 8 studies did not have statistically significant results, they provide relevant data because their relative risk estimates were consistent with the 16 studies that showed statistically significant results."); Siemiatycki Rep. at 64; Moorman Rep. at 29; Kane Rep. at 23-25.

The consistency of the data becomes obvious when statistical significance is considered along with all positive associations and the information gleaned from the confidence intervals. Graphically depicted, the information for case-control, cohort and the meta-analyses/pooled analyses is quite dramatic:

[TABLES START ON NEXT PAGE]

CASE-CONTROL STUDIES

Study	Relative Risk	Positive Association	CI consistent w/ 20% Increase	CI consistent w/ 25% Increase
Hartge (1983)	2.50	Yes*	Yes	Yes
Whittemore (1988)	1.45	Yes	Yes	Yes
Booth (1989)	1.30	Yes	Yes	Yes
Rosenblatt (1992)	1.70	Yes	Yes	Yes
Tzonou (1993)	1.05	Yes	Yes	Yes
Hartge & Stewart (1994)	0.30 (5-9 yrs.) 0.50 (10+ yrs.)	No	Yes	Yes
Wong (1999)	1.10	Yes	Yes	Yes
Cramer (1982)	1.92	Yes*	Yes	Yes
Harlow & Weiss (1989)	1.1	Yes	Yes	Yes
Harlow (1992)	1.50	Yes*	Yes	Yes
Chen (1992)	3.90	Yes	Yes	Yes
Purdie (1995)	1.27	Yes*	Yes	Yes
Green (1997)	1.30	Yes*	Yes	Yes
Shushan (1996)	1.97	Yes*	Yes	Yes
Chang and Risch (1997)	1.42	Yes*	Yes	Yes
Cook (1997)	1.60	Yes	Yes	Yes
Godard (1998)	2.49	Yes	Yes	Yes
Cramer (1999)	1.60	Yes*	Yes	Yes
Ness (2000)	1.50	Yes*	Yes	Yes
Mills (2004)	1.37	Yes*	Yes	Yes
Pike (2004)	1.60	Yes*	Yes	Yes
Jordan (2007)	1.00	Yes	Yes	Yes
Moorman (2009)	AA 1.19 Caucasian 1.04	Yes	Yes	Yes
Wu (2009)	1.53	Yes*	Yes	Yes
Rosenblatt (2011)	1.27	Yes	Yes	Yes
Kurta (2012)	1.40	Yes*	Yes	Yes
Wu (20015)	1.46	Yes*	Yes	Yes
Schildkraut (2016)	1.44	Yes*	Yes	Yes

COHORT STUDIES

Study	Relative Risk	Positive Association	CI consistent w/ 20% Increase	CI consistent w/ 25% Increase
Gertig (2000)	1.4 for Serous 1.09 for all EOC	Yes	Yes	Yes
Gates (2008)	1.24	Yes*	Yes	Yes
Gates (2010)	1.06	Yes	Yes	Yes
Houghton (2014)	1.12	Yes	Yes	Yes
Gonzalez (2016)	0.73	No	Yes	No

META-ANALYSES/POOLED ANALYSES

Study	Relative Risk	Positive Association	CI consistent w/ 20% Increase	CI consistent w/ 25% Increase
Harlow (1992)	1.30	Yes*	Yes	Yes
Gross (1995)	1.29	Yes*	Yes	Yes
Cramer (1999)	1.40	Yes*	Yes	Yes
Huncharek (2003)	1.33	Yes*	Yes	Yes
Langseth (2008)	1.35	Yes*	Yes	Yes
Terry (2013)	1.24 (EOC)	Yes*	Yes	Yes
Berge (2018)	1.22	Yes*	Yes	Yes
Penninkilampi (2018)	1.31 overall 1.25 cohorts serous invasive OC	Yes*	Yes	Yes
Taher (2018) (unpub.)	1.28	Yes*	Yes	Yes

This case, therefore, stands in stark contrast with the facts presented in the *Zoloft* case, which J&J cites repeatedly throughout its motion. In *Zoloft*, unlike here, there were no observational studies that demonstrated a statistically significant

association between *Zoloft* and birth defects.[303] In *Zoloft*, the district court considered whether in the total absence of any statistically significant results from any epidemiologic study, an expert could rely on "trends" to find causation.[304] The district court in *Zoloft* concluded that "[i]n general, before concluding that there is a 'true' association between a medication and an adverse outcome, the teratology community requires repeated, consistent, statistically significant human epidemiological findings, and studies which address suspected confounders and biases."[305] But, the Third Circuit in *Zoloft* refused to adopt such a bright-line rule.[306] The Third Circuit specifically noted that proving causality does not always require statistical significance.

> A causal connection may exist despite the lack of significant findings, due to issues such as random misclassification or insufficient power. Conversely, a causal connection may not exist despite the presence of significant findings. If a causal connection does not actually exist, significant findings can still occur due to, *inter alia*, inability to control for a confounding effect or detection bias. A standard based on replication of statistically significant findings obscures the essential issue: a causal connection. Given this, the requisite proof

[303] *In re Zoloft (Sertralinehydrochloride) Prod. Liab. Litig.*, 176 F. Supp. 3d 483, 498 (E.D. Pa. 2016).

[304] *In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 26 F. Supp. 3d at 455.

[305] *Id.* at 454.

[306] *In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d at 793.

> necessary to establish causation will vary greatly case by case.[307]

While the Third Circuit affirmed the exclusion of the expert in question, it disagreed that significance testing should be the sole metric that determined association.

Regardless of the "noise" that J&J makes about the *Zoloft* decision, and J&J's attachment to the importance of significance testing, what remains is that this case is not *Zoloft* and neither the PSC nor its experts "ignore" or "attack" statistical significance as a metric for assessing an association. And unlike in *Zoloft*, where there were no statistically significant studies, here, the majority of the studies are indeed statistically significant.

ii. "Significance testing" methodology urged by J&J is unreliable and rejected by the statistical and epidemiological communities

It would have been methodologically wrong to "significance test" the talc studies as J&J suggests should have been done. That methodology has been rejected by the statistical and epidemiologic communities

The American Statistical Association (ASA)[308] has *rejected* the use of "significance testing" outright. This rejection is both unambiguous and complete.

---

[307] *Id*. (footnote omitted).

[308] The ASA is "the world's largest community of statisticians, the "Big Tent for Statistics." https://www.amstat.org/ASA/about/home.aspx?hkey=6a706b5c-e60b-496b-b0c6-195c953ffdbc. Dr. Ballman, who is a statistician and not an

Just two months ago, in March 2019, the ASA devoted an *entire* supplemental volume of its journal *The American Statistician* to the persistent misuse of statistical significance as a metric for assessing an association. Indeed, the volume of *The American Statistician* was entitled "*Statistical Significance in the 21st Century; A World beyond P<0.05.*"[309] This Journal contained no less than 43 articles on the subject. Accompanying these 43 original articles were an editorial and a comment, with the comment appearing jointly in the journal *Nature*. Collectively, these 43 articles and the editorial and comment highlighted the error of "significance testing."

The important *Nature* comment article was co-authored by Sander Greenland, Ph.D. Dr. Greenland succinctly described and summarized the ASA's disapproval of "significance testing." Though J&J would paint Dr. Greenland as an outlier, this commentary was widespread in its acceptance and attracted *over 800 signatories in just 24 hours*. These signatories include scientists from the institutions from which J&J's experts hail (Weill Cornell, Yale, and Johns Hopkins).[310] In his review of the issue of "significance testing," the more than 800 scientist-signatories described the

---

epidemiologist, is a member and former officer of the ASA. *See Curriculum Vitae* of Karla Ballman, Ph.D. at 14, attached as **Exhibit 140**.

[309] 73 The American Statistician 1 (Supp. 1 2019), available at https://www.tandfonline.com/toc/utas20/current.

[310] Amrhein, *et al.* (2019). Dr. Greenland has been cited as an authority in the *Reference Manual on Scientific Evidence* and the textbook he-co-authored with Dr. Rothman, *Modern Epidemiology*, is cited as an authoritative text.

"significance" methodology embraced by J&J's experts as a "PERVASIVE PROBLEM" riddled with "errors" that "must stop":

> **PERVASIVE PROBLEM**:
>
> Let's be clear about what must stop: We should never conclude that there is 'no difference' or no association' just because a p value is larger than a threshold of .05 or equivalently because a confidence interval includes zero. **Neither should we conclude that two studies conflict because one has a statistically significant result and another did not. These errors waste research efforts and misinform policy decisions.**[311]

Faced with the definitive ASA consensus statement (published in March 2019, *after* all the experts had submitted their reports in this MDL), J&J dismisses it by its hollow criticism of one of the co-authors who it claims was a consulting expert[312] and pretends that this has no bearing on the attack that it makes here.[313] However, J&J half-heartedly attempts to defend the "significance testing" methodology by stating that abandoning it would diminish "statistical significance."[314]

---

[311] *Id.* at 305-6 (emphasis added).

[312] J&J takes a swipe at Dr. Greenland because he consulted with the PSC early in this litigation. *See*, Defs.' Mem. at 63, n. 152. The implication is ridiculous for numerous reasons, including the fact that over 800 scientists joined in, including scientists from the institutions form which J&J's own experts hail.

[313] Deposition of Gregory Diette, MD, MHS, April 9, 2019 ("Diette Dep.") at 313:17-20; 315:7-19, attached as **Exhibit 141**.

[314] Defs.' Mem. at 69-78.

But its methodology has long been rejected. In 2016, before the recent ASA publications (but after the *Reference Manual* called significance testing not "sophisticated"), the ASA took the unprecedented step of reminding scientists not to do "significance testing" for association by issuing an unprecedented consensus statement, "*Statement on Statistical Significance and P Values*."[315] Notably, the ASA deemed its unprecedented consensus statement on statistical methodology necessary because of the widespread and continued *misuse* of statistical significance in policy and the law. The ASA made clear that its consensus statement was designed to "shed light on an aspect of our field that is too often misunderstood and misused by the broader research community . . . ."[316] In the 2016 ASA Consensus Statement, the ASA discussed statistical significance testing and specifically warned of errors that could be derived from its misuse:

> Practices that reduce data analysis or scientific inferences to a mechanical bright line (such as p <.05) for justifying scientific claims or conclusions can lead to erroneous beliefs and poor decision making. A conclusion does not immediately become 'true' on one side of the divide and 'false' on the other.[317]

---

[315] *See generally* Wasserstein & Lazar, *The ASA's Statement on p-Values: Context, Process, and Purpose*, 70 Am. Statistician 129 (2016), attached as **Exhibit 142**. This 2016 ASA statement was cited in numerous reports by the PSC's experts against significance testing.

[316] *Id.* at 129.

[317] *Id.* at 131.

Moreover, the ASA cited longstanding literature against its use.[318] The epidemiologic community too has roundly and explicitly rejected it. In 1965 Professor Hill himself, addressed this issue in the very article that J&J claims is the standard methodology for causation recognized in this Circuit.[319] There, Professor Hill explained that: **"No formal tests of significance can answer these questions…they contribute nothing to the 'proof' of our hypothesis."**[320] Professor Hill further lamented in 1965 that some epidemiologists continued to erroneously apply significance testing, as J&J's and its experts do here.[321]

The admonition against "significance testing" is also taught to epidemiology students. For example, in the textbook *Modern Epidemiology*, the authors (Drs. Rothman, Lash, and Greenland)[322] address this error head-on. They characterize this methodology in no uncertain terms as "fallacious" and a "mistake":

> One mistake in implementing the consistency criterion is so common that it serves special mention. It is sometimes claimed that a set of literature is inconsistent simply because some results were "statistically significant" and some are not. **This sort of evaluation is completely**

[318] *Id*. at 132 (providing "a brief p-value and statistical significance reference list").

[319] Defs.' Mem. at 26-7.

[320] Hill (1965) at 299.

[321] *Id.*

[322] *See supra* n. 1.

> **fallacious even if one accepts the use of significance testing methods.**[323]

Moreover, other standard textbooks agree that the methodology is both misleading and unreliable.[324]

Far from being "generally accepted" as asserted by J&J and its experts, "significance testing" is unreliable and misleading and has gone from being merely "unsophisticated" to being outright disfavored. It is clearly inappropriate to grant a

---

[323] Rothman, *et al.*, *Modern Epidemiology* at 25 (emphasis added). Interestingly, J&J attempts to paint Dr. Rothman as an unreliable outlier. *See* Defs.' Mem. at 11, n. 20. Apart from the fact that he is widely cited in the Third Circuit, *see e.g*, *Deluca*, *supra*, his textbooks are cited in the *Reference Guide on Epidemiology* as one of the sources for epidemiology. *Ref. Man*. at 630. He is a founder of the leading journal, *Epidemiology*. https://www.bu.edu/sph/profile/kenneth-rothman/.

Indeed, 20 years ago, J&J consulted with Dr. Rothman with regard to its Talcum Powder Products and ovarian cancer, before much of the evidence at issue in this case was collected. Defs.' Mem. at 11, n. 20. Interestingly, J&J has not sought an update of Dr. Rothmans views on this relationship but instead has chosen litigation experts with far less experience in cancer epidemiology.

[324] For example, in the textbook *Epidemiology: Concepts and Methods*, the author states that "epidemiologists prefer using confidence intervals over statistical significance testing when it comes to assessing random error." William A. Oleckno, *Epidemiology: Concepts and Methods* at 222, 173, 221-24 (2008) attached as **Exhibit 143**. Similarly, in the textbook, *Introduction to Meta-Analysis*, Dr. Borenstein noted that it is wrong to "count[] the number of significant and nonsignificant p-values and pick[] the winner." Borenstein, *et al.*, *Introduction to Meta-Analysis* at 251. The textbook aptly explains the fallacy of J&J's experts' approach as follows: "The logic of vote counting says that significant finding is evidence that an effect exists, while the nonsignificant finding is evidence that an effect is absent. While the first statement is true, the second is not." *Id.* at 252 (emphasis added).

Daubert challenge against the PSC's general causation experts for failing to use a discredited "significance testing" methodology.

b. The PSC's causation experts properly assessed the strength and weaknesses of all the studies to analyze the talc-ovarian cancer association and properly did not adhere to a rigid hierarchy of evidence

J&J also criticizes the PSC's experts for allegedly failing to engage in a less than analytical methodology of further sorting the studies using a mechanical "hierarchy of evidence." Using this so-called hierarchy, J&J claims that the talc cohort studies (and their significance tested results) are to be automatically considered higher on the reliability hierarchy than the talc case-control studies.[325] As with statistical testing, and as demonstrated *infra*, J&J's and its experts' reliance on its rigid hierarchy is demonstrably wrong. While J&J posits its hierarchy as a "well established" epidemiologic principle, even the most basic epidemiology textbooks teach that there is not a rigid hierarchy.[326]

J&J's contention that the PSC's experts should have sorted the statistically significant/non-statistically significant results by a "hierarchy of evidence" is flawed because it ignores the strengths and weaknesses of each study. Moreover, this method is not supported by the *Reference Manual* (as J&J implies in its motion).[327]

[325] Defs.' Mem. at 5, 9-14, 47-67.

[326] Rothman, *et al.*, *Modern Epidemiology* at 111; Gordis, *Epidemiology* at 245, 257.

[327] Defs.' Mem. at 9 n. 16.

Indeed, it has been rejected by even the most basic epidemiologic textbooks as set forth in the *PSC's Motion to Exclude J&J's Epidemiology Experts*.[328]

i. The PSC's experts "even-handedly" considered the biases of both the cohort and case control studies

As independent scientists outside of litigation have done, *see e.g.* Health Canada Assessment, the PSC's experts reviewed both the case-control and cohort studies and have concluded that, on balance, there was a consistent association.[329] These conclusions were based on an analysis of the strengths and weaknesses of each talc study, regardless of whether they were case control or cohort [330] Despite the PSC's experts' review of the strengths and weaknesses of all talc studies, which is facially apparent by reviewing each of the PSC's expert reports, J&J nonetheless subjectively complains (as if arguing to a jury) that the PSC's experts were not "even handed in their approach.[331]

[328] *See PSC's Motion to Exclude Defendants' Epidemiology Experts* at 29-34.

[329] Kane Rep. at 9, 16; McTiernan Rep at 41-42, 64-65; Carson Rep. at 8, 9; Clark-Pearson Rep. at 6, 7; Smith Rep. at 16, 20; Siemiatycki Rep. at 64; Wolf Rep. at 6-7, 14-15; Plunkett Rep. at ¶ 71; Moorman Rep. at 11-15; Smith-Bindman Rep. at 38; Singh Rep. at 17, 53, 63.

[330] Kane Rep. at 8, 16-26; McTiernan Rep. at 22-24, 31-48; Clarke-Pearson Rep. at 2-3; Siemiatycki Rep. at 47-61; Wolf Rep. at 2-3, 6-7; Moorman Rep. at 15-29; Smith-Bindman Rep. at 16-18; Singh Rep. at 10-13, 27-53.

[331] Defs.' Mem. at 5.

Importantly, while J&J takes full opportunity to argue the "merits" of its case, it does not show that the PSC's experts failed to consider and address the potential for bias and confounding in the talcum powder-ovarian cancer studies. It does not do so because it cannot do so. The PSC's experts considered *and addressed* in detail whether there were biases in the talc specific studies (both case-control and cohort) that would likely have either biased them *towards* or *away* from a statistically significant association.[332] The PSC's experts' analysis in this regard was careful, analytical, consistent and even-handed. Any disagreement between J&J and any of

[332] *See, e.g.,* Siemiatycki Rep. at 69 ("There are various potential sources of bias in these studies, some of which could have inflated the true RR estimate and some of which would have deflated the true RR estimate. Apart from random measurement error, which is inevitable in such studies and which tends to deflate the RR estimates, there is no certainty that the other potential biases were in fact operative and to what degree. It is my opinion, however, that neither bias nor confounding explains the consistent positive association seen across studies.); McTiernan Report at 63-64 ("Viewed in the context of the high consistency of the study results across time, diverse study populations, and strong study designs, bias and chance as explanation for the increased risk are unlikely."); Kane Report at 9 ("The vast majority of studies and meta-analyses find an association with an increased risk of ovarian cancer. Under these circumstances, viewing the evidence as a whole, the likelihood that the consistent finding of an association can be explained by bias, or chance or confounding is highly unlikely, especially in light of the results of the other lines of evidence."); Moorman Report at 10 ("I considered the potential biases of individual studies, both those that supported and those that did not support an association between talc and ovarian cancer, and how those biases may have impacted the findings. . . . some biases have the potential to lead to an overestimate of the relative risk (e.g. recall bias in case-control studies) while others could result in an underestimate of the relative risk (e.g. incomplete ascertainment of talc use in the cohort studies).); Singh Report at 54 ("Recall bias is less likely to occur for chronic daily exposures such as talc as compared to intermittent short exposures.").

the PSC's experts with regard to the weight to be accorded to any of the biases and confounders, in the end, is not an issue of reliability but is an issue to be explored during cross-examination.

While J&J purports to base its criticism on a "hierarchy of evidence," the real basis for its attack is simply that the PSC's experts did not sort studies as J&J's experts chose to do. Indeed, J&J's argument goes on endlessly about why its own litigation experts believe that there were biases and confounding that may have created a spurious (but statistically significant) association in the talc case-control studies. J&J supports this contention by citing repeatedly to their own experts' reports (primarily Drs. Diette, Merlo, Holcomb and Ballman).

This issue was squarely before the court in the *Roundup* MDL.[333] In that case, as here, there were both case control studies, pooled studies, and 3 meta-analyses as well as a cohort study that addressed the relationship between Roundup (glyphosate) and Non-Hodgkin's Lymphoma (NHL). As here, the defendant, Monsanto, "raised concerns about basing a causation assessment on case control studies and meta-analyses," noting that case control studies were prone to "recall bias."[334] They also raised the issue of "important confounders."[335] Instead of the case control studies,

[333] *In re Roundup Prods. Liab. Litig.*, 2018 WL 3368534 (N.D. Cal. July 10, 2018).

[334] *Id.* at *11

[335] *Id.* at *13.

Monsanto in *Roundup* urged that a cohort study (called the AHS study), which did not show a statistically significant association, was more reliable. Since, according to Monsanto, cohort studies allegedly avoided the biases inherent in case-control studies, Monsanto sought to exclude the plaintiffs' experts as unreliable under *Daubert*. Specifically, Monsanto argued that the AHS study was reliable because of its design, and the case control-studies and meta-analyses relied on by plaintiffs' experts, were not.[336]

What ensued was a vigorous debate between the parties as to the reliability of the competing epidemiologic evidence. On one hand, Monsanto argued (as J&J does here) that the case-control studies were less reliable because they were subject to bias and confounding.[337] On the other hand, the plaintiffs' experts argued that the cohort study was less reliable because of "exposure misclassification" based on an initial survey and (unlike *any* of the talc cohort studies in the case) a follow-up questionnaire provided to study participants during the course of the study.[338] The *Roundup* court implicitly rejected the "cohort is better than case control" argument that J&J advances here:

> The upshot of all this is that the epidemiology evidence is open to different interpretations, and the potential flaws in the data from the case-control studies and meta-analyses

[336] *Id.* at *13-14.

[337] *Id.* at *11-14.

[338] *Id.* at *13.

> are not overwhelmingly greater than the potential flaws in the data from the AHS study. An expert operating "within the range of accepted standards governing how scientists conduct their research and reach their conclusions" could thus place less weight on the AHS study, and could conclude that the analyses of the case-control studies support an association between glyphosate exposure and NHL, even if this is not necessarily the best interpretation of the evidence. *Daubert II*, 43 F.3d at 1317. As a result, an expert who places more weight on the case-control studies than the AHS study cannot be excluded as categorically unreliable for doing so.[339]

The parallel between *Roundup* and this case is readily apparent.[340] Here, the PSC's causation experts did not just reflexively assume one study design was better than the other with respect to the ovarian cancer question, as J&J contends. Rather, they specifically and methodically reviewed each study and category of studies for strengths and weaknesses. They considered:

- Whether the case control studies were likely due to *recall bias*. They concluded that this was unlikely,[341] a

[339] *Id.* at *15 (emphasis added).

[340] The cases are parallel with one important exception. Unlike the defense experts in *Roundup*, J&J's causation experts admittedly relied heavily on a superficial "hierarchy" to support its views and not a detailed analysis of the strengths and weaknesses of the talc studies regardless of design.

[341] McTiernan Rep. at 24 ("For the case-control studies, media reports of associations between talc and ovarian cancer could have influenced cases such that they recalled use of talcum powder products to a greater degree than controls. However, the studies for which data collection pre-dated news reports of this association showed similar effects to those for which data were collected afterward. Thus, "recall bias" is unlikely to be an issue. As mentioned above, recall bias is a theoretical bias; studies that have investigated other sources of data on exposures have failed to confirm the presence of differential recall between cases and controls.");

> conclusion that has also been noted in the medical literature relating specifically to the talc-ovarian cancer studies.[342]

Siemiatycki Rep. at 54-55; Moorman Rep. at 21-24; Singh Report at 54 ("Recall bias is less likely to occur for chronic daily exposures such as talc as compared to intermittent short exposures."); Kane Rep. at 9, 17-28; Carson Dep. at 240:19 to 241:20 ("you can fault case-control studies for being particularly sensitive to recall bias, but many of these authors who perform these studies indicated that they were well aware of that bias potential and took measures to avoid it."); Smith Report at 16 (Recall and confounding bias in case-control studies appear to have minimal impact.)."); Clarke-Pearson Dep. at 164:14-20; Smith-Bindman Report at 17; *See also* Deposition of Ellen Blair Smith, MD, January 9, 2019 ("Smith Dep.") at 186:23 to 187:22 ("I quoted the part of the paper where the author specifically adressed concerns about recall bias and found them unlikely."), attached as **Exhibit 144**; Wolf Rep. at 8; *see also* Wolf Dep. at 254:5 to 255:12, 310:18 to 311:20, 313:6 to 313:21 (" In all of the studies, I review the methodology, I look for any evidence of bias, recall bias or anything else. Not every study compared before 2014 and after 2014. This one did, they found no significant difference in recall of use.")

[342] Schildkraut (2016) ("our data do not support that recall bias alone before 2014 verses 2014 of later would account for the association with body powder use and EOC"); Gates (2008) ("In addition, the exposure definition of genital talc use at least once per week may have decreased the influence of recall bias in this analysis since habitual talc use is likely to be recalled more accurately than sporadic use."); Health Canada Assessment ("In studies where the exposure is simple (e.g., never versus ever use), recall bias is unlikely to be an important source of bias. The positive association is strongest for the serous histologic type (Berge *et al.* 2018; Taher *et al.* 2018); findings that the association may vary by histologic type detracts from the hypothesis of report bias, as the type of bias would likely operate for all histologic types"); Langseth (2008) ("Methodological factors such as recall bias should always be considered in case-control studies. It could have been a problem had there been wide-spread publicity about the possible association between use of body powder and cancer. The International Agency for Research on Cancer (IARC) the working group considers that there has not been widespread public concern about this issue and therefore considers it unlikely that such a bias could explain the consistent findings."); Mills (2004) ("Recall bias has also been implicated as a limitation in studies of talc and ovarian cancer. However, findings in a prospective study, the Nurses' Health Study, in which exposure data were collected prior to diagnosis and hence free of recall bias, were similar to the present study finding for talc use and

> Whether the case control studies were subject to uncontrolled for confounding. They concluded that this was unlikely,[343] an observation that has also been made in the medical literature.[344]

---

serous invasive ovarian cancer. It has also been suggested that use of talc is habitual *versus* memorable and not likely to be subject to recall bias.").

[343] McTiernan Rep. at 15, 24, 31; Siemiatycki Rep. at 59-60; Moorman Rep. at 28-29 ("Although uncontrolled confounding is a theoretical possibility, to my knowledge, in the more than 30 years of research on talc and ovarian cancer no such confounder has been identified that could account for the increased risk associated with talc use."); Singh Report at 12, 25, 34, 46, 54, 60 (discussing confounding in general and in relation to individual studies); Singh Dep. at 254:5-12; Singh Rep. at 54 ("Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. To invalidate the statistically significant findings of an increased risk of ovarian cancer from the studies, one would have to postulate a degree of selection, recall bias and confounding pervasive across different time periods, different populations which is highly implausible."); Kane Rep. at 9; Carson Report at 8 ("Most, but not all, of these studies show a consistent positive relationship. When confounding and bias are exhaustively considered, the positive association remains."); Clarke-Pearson Dep. at 118:13-119:21 ("Uncontrolled confounding is a potential concern in case-control studies, is that right? Yes, but if your controls are well selected then that negates much of the bias.); Smith-Bindman Report at 32: ("Studies were not included if they reported only crude ORs unadjusted for confounding factors); Smith Report at p. 16 ("Recall and confounding bias in case-control studies appear to have minimal impact."); Wolf Report at 8.

[344] *See also* Narod (2016) at 2 ("It is unlikely that the association between talc and ovarian cancer is due to confounding and so it is fair to say that if there is a statistically robust relationship between talc use and ovarian cancer it is likely to be causal (albeit with intermediate factors such as inflammation)); Cramer (2016) at 345 ("Among many epidemiological variable, no confounders for the association were identified"); Cramer (1999) at 356 ("In summary, we have demonstrated a consistent association between talc and ovarian cancer that appears unlikely to be explained by recall or confounding.").

> As they did with case-control studies, the PSC's experts also considered the strengths and weaknesses of the cohort studies. Specifically, they considered:Whether the Cohort Studies were designed to study the ovarian cancer-talcum association. (They were not).[345]

---

[345] McTiernan Rep. at 64 ("While the cohort studies on average showed more attenuated relative risks of ovarian cancer in relation to use of talcum powder product use, these studies were not well designed to determine true risk for ovarian cancer and perineal talc use."); Singh Rep. at 10-11 ("In contrast, prospective cohort studies may be limited by the short-duration of follow-up which may be insufficient to ascertain the effect of exposure on long-term outcomes and bias their findings towards the null. Secondly, for relatively rare diseases, such as ovarian cancer, case-control studies are more efficient. Because we are looking at the incidence of disease between the two arms of a study, a cohort study may have limited statistical power regardless of the actual number of subjects enrolled if the number of cases is small. For example, the Nurses' Health Study recruited almost 80,000 participants for only 307 cases of ovarian cancer."); Singh Rep. at 47 ("…it is important to emphasize that none of the cohort studies discussed below were designed to evaluate the association between talc use and ovarian cancer at the time of cohort assembly. In other words, evaluating the association between talc use and ovarian cancer was not the a-priori primary objective of the study but evaluated as a subsequent hypothesis, with its inherent limitations. For example, the NHS cohort was assembled in 1976 but data on talc use was not collected until 1982. In contrast the primary objective of most case-control studies noted above was to evaluate the risk of ovarian cancer associated with talc use."); Kane Rep. at 24 ("Cohort studies begin when all participants are free of the disease in question. After a follow-up period, those that have the disease being studied are compared by exposure risk being studied to those who did not develop the disease. Although this helps to ensure exposure predates disease, there may be a lack of data if the disease is rare or if there is a long latency period between exposure and disease presentation/diagnosis, as is the case of ovarian cancer and talc."); Carson Dep. at 251:4 to 252:1; Clarke-Pearson Dep. at 144:7-17 ("the cohort studies were not designed to answer that question. They're poorly done and I don't think contribute to this discussion."); Smith-Bindman Report at 19-22.; Smith Report at 14-15; Wolf Dep. at 256:19 to 257:12 ("the primary endpoints of the Nurses Health Study and the Women's Health Study were not to look at the relationship of talc and ovarian cancer."); Deposition of Jack Siemiatycki, MSc, PhD, January 31, 2019 ("Siemiatycki Dep.") at 171:2-13 (it's mainly a problem for cohort studies. And if you carry out a cohort study of – focused on cancer, and you

- Whether there was a substantial risk of exposure misclassification which would tend to bias these studies towards showing no association.[346] They concluded that this risk was substantial since the cohort authors in the case asked about talc exposure one time and conducted no follow up for years to determine whether the behavior had changed.[347] This significant limitation was noted by many looking at the talc cohort studies.[348]

---

collect information about exposure, and then follow them for two years to find out how many of them got cancer, and whether there is a difference between the people who were exposed and the people who are not exposed, well, that would be pretty hopeless because it takes more than two years for cancers to develop and be diagnosed. So short follow-up periods in cohort studies would be a source of bias in cohort studies."), attached as **Exhibit 145**.

[346] Misclassification bias is "[t]he erroneous classification of an individual in a study as exposed to the agent when the individual was not, or incorrectly classifying a study individual with regard to disease." *Ref. Man*. at 624.

[347] McTiernan Rep. at 16-17, 19, 43, 46; Siemiatycki Rep. at 56 ("The women in the cohort studies were "locked into" their exposure category at baseline of the cohort study. If there were women who in fact started using powders after the baseline, they would be incorrectly labelled as non-users. And, if there were indeed a risk associated with use of talc powders, the risk estimate would be diluted by the incorrect inclusion of users among non-users. Accordingly, the longer such subjects are followed, the more likely such misclassification is to occur."); Moorman Rep. at 26 ("Each of the cohort studies assessed talc use at a single point in time and did not update the information at subsequent follow-up interviews."); Singh Report at 10-11; Kane Report 24; Carson Dep. at 251:4 to 252:1; Clarke-Pearson Dep. at 144:7-17; *see also* 164:2-11; Smith-Bindman Report at 19-22.; Smith Report at 14-15; Wolf Report at 7-8; *see also* Wolf Dep. at 256:19 to 257:12 ("two of the three studies are limited by the documentation of how much -- how often and how frequent powder was used.").

[348] Gates (2008) at 2443 ("Information on talc use was only collected in 1982 in the NHS, so it is possible that some participants were misclassified with respect to their talc use history.") Gates (2010) at 52 ("The incomplete data for a few exposures, in particular talc use and family history of ovarian cancer, also are weaknesses because the limited data may have influenced the observed associations for these exposures.

- Whether the studies accounted for the long latency period of ovarian cancer. They concluded that this was a weakness of these studies.[349]

- Whether the studies had enough participants (were adequately "powered") to study the ovarian cancer risk. They concluded that this was a substantial weakness, particularly of the Gonzalez (Sisters Study) which followed this cohort for a little over 6 years.[350]

The association with talc use in our analysis differed from the association in a previous analysis of the NHS cohort (34), possibly because of a greater degree of exposure misclassification over 24 years of follow up."). The Taher (2018) meta-analysis, the authors stated that "[i]t is possible that women who were not exposed to perineal talc at the time of cohort entry began using talc at a later time, and vice versa, possibly introducing non-differential misclassification of exposure, which could bias the risk estimate towards the null value of unity." Taher (2018) at 44.

[349] McTiernan Rep. at 47; Siemiatycki Rep. at 57; Moorman Rep. at 27 ("As the authors [of the Sister Study] acknowledged in their paper, if latency (the time between exposure and diagnosis of cancer) is 15 to 20 years, the exposure assessments do not accurately reflect the period of risk."); Singh Rep. at 52, 55; Kane Rep. at 24, 26; Carson Dep. at 168:5 to 168:9 ("There may have been higher rates of ovarian cancers, but you have to also understand that the latency period for ovarian cancer is pretty long. It's greater than 20 years, often as long as 40 years."); Clarke-Pearson Report at 8; Smith-Bindman Report at 17 (several had very short follow-up periods with data or information about the time before the cancer occurred. This negates an advantage of cohort studies."); Smith Report at 14-15 ("With an expected latency period of over twenty years, this study would not pick up all cases."); Wolf Report at 7-8 ("the short follow-up fails to account for the latency period.").

[350] McTiernan Rep. at 46-48 ("The sample sizes (numbers of cases) of most of the cohort study publications were likely too small to be able to detect a relative risk in the order of 1.24 (the value found in the Terry pooled analysis) with reasonable power, especially for different histologic subtypes."); Moorman Rep. at 25 ("As described in a commentary by Narod, the lack of a significant overall association between ever use of talc and ovarian cancer in the cohort studies may be due to the fact that the despite the large size of the cohorts, the studies were not adequately powered to detect a relative risk of approximately 1.2."); Singh Rep. at 10-11 ("Secondly, for relatively rare diseases, such as ovarian cancer, case-control studies

While J&J's motion (and certainly its experts) pretend otherwise, the weaknesses of the cohort studies are significant and were independently criticized in the scientific literature and by regulatory bodies. Taher (2018) came to the exact conclusion about the weakness of the cohort studies reached by the PSC's experts:

> Although cohort study designs are efficient for examining diseases with a long latency period, it is essential that the period between talc exposure and the cancer diagnosis be sufficiently long. Gonzalez *et al.* suggested that the latency period for ovarian cancer is between 15 to 20 years. In the cohort studies included in this review, Houghton *et al.* reported a mean follow up of 12.4 years while Gates *et al.* followed a cohort of women for 24 years. Gertig *et al.* and Gonzalez *et al.* noted that one of their studies' main limitations was the relatively short follow up periods that may not be adequate to detect a potential association between talc exposure and 468 ovarian cancer.

---

are more efficient. Because we are looking at the incidence of disease between the two arms of a study, a cohort study may have limited statistical power regardless of the actual number of subjects enrolled if the number of cases is small. For example, the Nurses' Health Study recruited almost 80,000 participants for only 307 cases of ovarian cancer."); Carson Dep. at 251:4 to 252:1; *see also* 252:19 to 253:3 ("I think by and large most cohort studies are underpowered."); Clarke-Pearson Dep. at 164:2-11; Smith-Bindman Report at 20-21; Smith Report at 14-15 ("All of the cohort studies are limited by failure to obtain complete information, lack of power, selection bias, and short follow-up."); Wolf Report at 6-8 ("All of the cohort studies are limited by lack of power, failure to make the appropriate queries, selection bias, and short follow-up."); *see also* Taher (2018) ("In addition, cohort studies included may have been underpowered to detect an odds ratio (relative risk) of 1.3 estimated from the case control studies. This was noted by Narod *et al.*, who suggest that cohorts of at least 200,000 women would be needed to reach statistical significance if the true odds ratio is 1.3. The cohort studies included in this review included much smaller cohort sizes, ranging between 41,654 and 78,630 women.")

> In addition, cohort studies included may have been underpowered to detect an odds ratio (relative risk) of 1.3 estimated from the case control studies. This was noted by Narod *et al*., who suggest that cohorts of at least 200,000 women would be needed to reach statistical significance if the true odds ratio is 1.3. The cohort studies included in this review included much smaller cohort sizes, ranging between 41,654 and 78,630 women.
>
> Finally, in cohort studies, talc exposure was assessed at cohort entry and was used as a measure of chronic talc use during follow up. It is possible that women who were not exposed to perineal talc at the time of cohort entry began using talc at a later time, and vice versa, possibly introducing non-differential misclassification of exposure, which could bias the risk estimate towards the null value of unity. Conversely, in the presence of differential exposure misclassification, a bias away from the null hypothesis could accentuate differences between the cohort and case-control studies.[351]

As in *Roundup*, the PSC's experts in this case have adequately explored the strength and weaknesses of all relevant studies of all designs. That they conclude that, on balance, the case-control studies provide stronger evidence of the association than the cohort studies in this case (which also showed a positive association, *albeit* not a statistically significant one) is a reliable opinion to present to a jury. Indeed, that reasonableness is strengthened because a meta-analysis of the cohort studies (Penninkilampi) has demonstrated a statistically significant increased risk of Serous Invasive Ovarian Cancer. "As it stands, a meta-analysis of observational studies such

[351] Taher (2018) at 43-44.

as the present study provides the highest level of evidence practically feasible for this research question."[352]

ii. "Hierarchy of evidence" sorting by generic study type as urged by J&J is itself an improper methodology

Knowing full well that the PSC's experts did in fact explore the weaknesses of all the talc-ovarian cancer studies regardless of design, J&J implies that they should have simply prioritized them by study designs. According to J&J, it was a methodologic error generally to "elevate[] the importance of studies that are prone to bias and confounding [case control] over those that are generally deemed more reliable by the medical community [cohort]."[353] J&J asserts that there is a "hierarchy of evidence" that includes "in descending order of reliability—cohort studies, case control studies, and cross sectional studies." [354]

J&J also falsely implies that its view of the "hierarchy" is endorsed in the *Reference Manual* [355] To be clear, the "hierarchy" described in the *Reference Manual* does not distinguish between cohort and case control studies. To the contrary, it specifically assigns them the same weight stating simply that:

---

[352] Penninkilampi (2018).

[353] Defs.' Mem. at 9.

[354] *Id.* at 10.

[355] *Id.* at 11-12, *see also* n.16.

> When ordered from strongest to weakest, systematic review of randomized trials (meta-analysis) is at the top, followed by single randomized trials, ***systematic reviews of observational studies, single observational studies,*** physiological studies, and unsystematic clinical observations.[356]

There is good reason why the *Reference Manual* does not state that "cohort studies" are more reliable than "case control studies." Simply, because they are not. In fact, the hierarchy methodology (like that employed by J&J's experts) has been derided as a "substitute for more thoughtful and difficult tasks" of evaluating the strengths and weaknesses of individual studies.[357]

In Dr. Rothman's paper, "*Six Persistent Research Misconceptions*" referred to above, he also addresses the so-called "hierarchy of evidence" that J&J declares is a "fundamental epidemiologic principle." In this paper, Dr. Rothman listed J&J's "hierarchy of evidence" as the very first research misconception, which he describes as follows: "[t]here is a hierarchy of study designs: randomized trials provide the greatest validity, followed by cohort studies, with case-control studies being least reliable."[358]

According to this epidemiologic review, J&J's superficial methodology of simply ranking studies generically by general study design -- is flawed and leads to

---

[356] *Id*. at 724-5 (emphasis added)

[357] Rothman, *Six Persistent Research Misconceptions* at 1066.

[358] *Id.* at 1061.

error. As Dr. Rothman explained: "[D]iscrepancies between cohort studies and case control studies should *not* be explained away superficially by a presumed advantage of cohort studies over case-control studies."[359] Indeed, he stated that "both cohort and case-control studies will yield valid results when properly designed and carried out."[360] He further stated that it is wrong to "disparage" case-control studies and that "study design should not be taken as a guide to a study's validity."[361]

Importantly, J&J *in particular* should know that the superficial methodology it urges as a "fundamental principle" is flawed since it previously hired Dr. Rothman who told them so.[362] In 2000, J&J (through Defendant PCPC) commissioned Dr. Rothman to do a causation analysis on talcum powder-ovarian cancer for the National Toxicology Program (NTP). In that analysis. Dr. Rothman made clear that epidemiologists outside the courtroom reject the very study design "hierarchy" that J&J presents here in this litigation as "generally accepted." While his analysis of the talc evidence itself is almost 20 years old and significantly dated (by way of example, it does not include the past 19 years' worth of additional observational evidence on talcum powder and ovarian cancer and does not include information about cosmetic

[359] *Id.* at 1061.

[360] *Id.* at 1060.

[361] *Id.* at 1061.

[362] Kenneth J. Rothman, et al. *Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer* at 3 (Nov. 28, 2000), IMERYS 209695, attached as **Exhibit 146**.

powders containing asbestos), his general view about J&J's so-called "hierarchy of evidence" sorting principle is not:

> **It is commonly believed that the validity of case-control studies is worse than cohort studies, but this view is mistaken. The validity of a study depends on the specifics of the study design, the nature of the data, and the nature of the hypothesis that the study addresses.** For example, a cohort study that examines the long-term risk of cancer among coffee drinkers after a one-time dietary assessment of coffee consumption would suffer from weak exposure assessment. Although the exposure information may have been accurate for the time it was collected, the exposure status of cohort members will change with time and the initial measure might be only poorly correlated with a more meaningful measure of coffee consumption. The effect of having a poor measure of coffee consumption will be considerable non differential misclassification, a type of error that introduces bias into study results that tends to drive effect estimates towards the null condition of no effect. In contrast, it may be possible to get more detailed exposure information from study subjects in a case-control study, which might avoid some of the bias that would result from a cohort study.[363]

This same observation was noted in the textbook *Epidemiology*, written by Leon Gordis, MD, professor of epidemiology at Johns Hopkins and a co-author of the *Reference Guide on Epidemiology* in the *Reference Manual* on Scientific Evidence.[364] As set forth in the *Reference Manual*, Dr. Gordis' textbook categorized

[363] *Id.*

[364] Leon Gordis, *Epidemiology*.

both cohort and case-control studies as having the *same* level of reliability.[365] The methodology employed by the PSC's experts in evaluating relevant observational studies is generally accepted. What is clear is that the "hierarchy of evidence" methodology employed by the J&J's experts is "junk-science" that this Court should prohibit from entering the courtroom. It cannot be the basis for the exclusion of the PSC's experts.

D. THE STRENGTH OF ASSOCIATION ASPECT OF THE BRADFORD-HILL CAUSATION GUIDELINES IS MET BY THE 25-45% STATISTICALLY SIGNIFICANT OVERALL RISK OF OVARIAN CANCER

One of J&J's central arguments that repeats throughout its Memorandum—is that the PSC's causation experts *defined* the consistent 25-45% increased risk seen in the epidemiologic literature magnitude as "strong" when, according to J&J, that association is "weak."[366] That alone, according to J&J, "highlights the unreliability of [the PSC's causation experts' methodology]."[367,]

J&J then argues that the PSC's experts somehow ignored 1) "significant evidence" that the consistent association seen over four (4) decades might have been

---

[365] *Id.* at 245, 257.

[366] Defs.' Mem. at 1, 31-47. J&J describes the association as "weak" over 30 times in the first half of their motion.

[367] According to J&J "the mere fact that plaintiffs' experts opine that strength of association supports a causal conclusion based on an objectively weak magnitude of the risk itself highlights the unreliability of their methodology." *Id.* at 34.

the result of "recall bias";[368] and 2) that some other unidentified confounding factor might have been or could have been a confounding variable for these studies.[369]

As set forth below, neither of these claims have merit.

1. J&J's Argument Over Whether the Talc-Ovarian Cancer Risk that is One that is "Small," "Medium" or "Strong," is a Red-Herring

J&J's argument over whether the increased risk that exists is one that is "small," "medium" or "strong," is a red-herring. As long as the risk is greater than 1.0, there is no minimal threshold for a causal relationship. As noted in the *Reference Manual*: "While strength is a guideline for drawing an inference on causation from association… there is no specified threshold required."[370]

This point is made in even the most basic textbooks on epidemiology. As noted by Rothman in *Modern Epidemiology*: "[A] strong association is neither necessary nor sufficient for causality, and [] weakness is neither necessary nor sufficient for absence of causality" using as examples, "smoking and cardiovascular disease or between environmental tobacco smoke and lung cancer [which are] accepted by most as causal even though the associations are considered weak."[371]

---

[368] *Id.* at 35-38.

[369] *Id.* at 38-40.

[370] *Ref. Man*. at 611, n. 186.

[371] Rothman, *et al., Modern Epidemiology* at 26.

Indeed, as explained in *Section IV(D)(1)(b), infra*, there are many recognized causal relationships that have Odds Ratios less than 2.0.

Indeed, even J&J's experts themselves concede that there is no universal "numeric definition" or "hard threshold" for strength and there is "no cut off value for the magnitude of an association between exposure required or the relationship to be causal."[372] Dr. Diette agreed that "there is no absolute cutoff to define a large versus small relative risk..." and the "size of the risk does not, in itself, determine causation."[373]

The arbitrariness of J&J's insistence that various risk ratios are capable of being categorized as "strong," "moderate" or "weak" is borne out by the inconsistency between J&J's experts' opinions and evidence they rely on. J&J and its experts would like it to be a principle of epidemiology that a risk ratio of less than 2.0 is categorically a "weak" risk, even suggesting that there is a "consensus" about this. However, the NCI assessment upon which J&J and its experts rely for this "consensus" has characterized the relative risks of obesity and ovarian cancer (RR 1.1) and Hormone Replacement Therapy and ovarian cancer (RR 1.2-1.8) as

[372] Report of Karla Ballman, PhD, February 25, 2019 ("Ballman Rep.") at 22, attached as **Exhibit 147**; Report of Christian Merlo, MD, PhD, February 25, 2019 ("Merlo Rep.") at 43, attached as **Exhibit 148**.

[373] Report of Gregory Diette, MD, MHS, February 25, 2019 ("Diette Rep.") at 7, attached as **Exhibit 149**.

"moderate", clearly demonstrating that a risk ratio below 2.0 can and does qualify as a risk that is stronger than "weak."[374] This demonstrates that it is the risk estimates themselves that matter, not some arbitrary description of them as being "strong," "moderate" or "weak."

a. The PSC's experts did not define the talcum powder ovarian cancer association as "small," "moderate" or "strong" association

Despite J&J's attempts to force the PSC's experts to define the magnitude of association as strong, moderate or weak, the PSC's experts did not do so because (as J&J's experts agree), these are *subjective* terms without any recognized *objective* epidemiologic definition.[375] Rather than classifying the association according to

[374] National Cancer Institute, *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)-Health Professional Version*, at 3, attached as **Exhibit 150**; Merlo Rep. at 45.

[375] *See infra* n. 366. McTiernan Dep. at 228:18-24; Moorman Dep. at 249:3-14; Siemiatycki Dep. at 147:2-148:19; Carson Depo at 230:18 to 231:5 and 232:13 to 233:23 ("A 30% increase may be classified by epidemiologists as weak or modest, but if you look at the number of women in this country who die each year from this fatal disease, that represents about 3,000 lives that could potentially be saved through prevention."); Clarke-Pearson Dep. at 128:15 to 131:1 (I'm not aware that it's a strong association or a weak association. It's a statistically significant association,'); Smith-Bindman Dep. at 235:24-237:5 ("He doesn't quantify it as weak or strong, but there's a suggestion that a 39 percent increase is important."); Smith Dep. at 176:24 to 177:10 ("modest, weak suggests unimportant, and I would not call it unimportant."); Wolf Dep. at 368:3 to 368:20 and 226:7 to 228:19 ("studies as a whole, 1.3 to 1.4 odds ratio. And do you consider that to be a strong association? I consider it to be a consistent, reliable association. It doesn't have to be a high number.").

J&J's artificial and subjective definition, the PSC's experts mostly resisted those attempts and defined the associations epidemiologically and by what the evidence actually shows. Specifically, the PSC's experts found a 25-45% increased risk but did not define that percentage range of risk as being "strong" or otherwise.

In their reports, each of the PSC's causation experts described the overall talc–ovarian cancer association as what it is—a 25-45% increased risk.[376] At deposition, it was clear that J&J's legal strategy was to push each PSC expert to quantify the magnitude of this risk as "strong."[377] However, the PSC's experts refused to agree

[376] McTiernan Rep. at 8, 63 (22-31%); Siemiatycki Rep. at 38-39, 47-48, 69 (28%); Plunkett Rep. at 49 (~30%); Moorman Rep. at 39 (25-30%); Singh Rep. at 62-63 (30-60%); Kane Dep. at 190:15-20 (30-40%); Carson Dep. at 232:13 to 233:23 ("Q. When you say 30% increased risk, that's a 1.3 odds ratio, is that right? A. That's correct."); Clarke-Pearson Report at 6 ("the data shows a consistent statistically significant increased risk of developing EOC with perineal talcum powder use. Overall, the risk is increased 20-60% when compared with women who didn't not use talcum powder."); Smith-Bindman Report at 27 ("The systematic reviews provide a remarkably consistent estimate of an approximately 30% increase in the risk of ovarian cancer associated with any talc powder products use."); Smith Report at 16 ("When looking at epidemiological studies with a critical eye and in their totality, they demonstrate a clear, consistent, and statistically significant increased risk of EOC (approximately 20-50%) with the genital use of talcum powder products."); Wolf Report at 8 ("the risk elevation is 20-60%).

[377] McTiernan Dep. at 228:18-24 ("Q . . . Do you think that relative risks of 1.06 and 1.12 are weak? strong? moderate? How would you characterize those numbers? . . . [A]: I tend to look at the number of what they are, rather than giving an adjective to it."); Singh Dep. at 140:19-23 ("Q. Can you point to any peer-reviewed literature on talc and ovarian cancer that states that 1.3 odds ratio is a strong association? A. Again, that's not -- I'm not looking at talc at 1.3 is a strong association."); Moorman Dep. at 249:3-14 (". . . there is no absolute terminology that would say what is a weak association, what is modest, and what is strong. So I think it is more accurate

with J&J's effort to characterize testimony out of context. As Dr. Moorman testified when pressed on the subject:

> Q. And I think you are conflating—or you are misunderstanding my question, because you are answering the question about whether the association is real or not real, and, my question for you is whether the association is weak, modest or strong. How would you characterize it?

---

to describe it as it is, a 20 to 30 percent increased risk of ovarian cancer."); Siemiatycki Dep. at 147:2-148:19 ("The terminology around strength of association -- weak, modest, strong, very strong, medium, et cetera – it doesn't have -- there are no regulations. There's no epidemiologic handbook that says if a relative risk is in this range, you call it weak or moderate and so forth. So the term "moderate" -- actually, the terminology around strength of associations was probably most influenced by the smoking and lung cancer situation in the '50s and '60s where there were relative risks of ten approximately, ten times as high of risk for smokers as for nonsmokers of getting lung cancer, and that was considered a benchmark for strong associations.... It has subsequently turned out that the level of relative risk for smoking and lung cancer is exceptional among known carcinogens, and that this -- there are not many that have such high relative risks. I'm just giving you a bit of background because the terminology is controversial, and I know it plays into the case of how we -- how we characterize the associations around talc and ovarian cancer . . . . So where you draw the line between strong, moderate, weak, and so on, is a kind of -- is a vague notion."); Carson Dep. at 230:18 to 231:5 and 232:13 to 233:23 ("A 30% increase may be classified by epidemiologists as weak or modest, but if you look at the number of women in this country who die each year from this fatal disease, that represents about 3,000 lives that could potentially be saved through prevention."); Clarke-Pearson Dep. at 128:15 to 131:1 (I'm not aware that it's a strong association or a weak association. It's a statistically significant association,'); Smith-Bindman Dep. at 235:25-237:5 ("He doesn't quantify it as weak or strong, but there's a suggestion that a 39 percent increase is important."); Smith Dep. at 176:24-177:10 (Modest, weak suggests unimportant, and I would not call it unimportant."); Wolf Dep. at 368:3-20, 226:7- 228:19 ("studies as a whole, 1.3 to 1.4 odds ratio. And do you consider that to be a strong association? I consider it to be a consistent, reliable association. It doesn't have to be a high number.")

> A. And I would—as I have said, there is no absolute terminology that would say what is a weak association, what is modest, and what is strong. So I think its accurate to describe it as it is, a 20-30 percent increased risk of ovarian cancer.[378]

Dr. Siemiatycki was also pressed but refused to use the J&J lawyer's definition stating that:

> The terminology around strength of association -- weak, modest, strong, very strong, medium, et cetera – it doesn't have -- there are no regulations. There's no epidemiologic handbook that says if a relative risk is in this range, you call it weak or moderate and so forth. So the term "moderate" -- actually, the terminology around strength of associations was probably most influenced by the smoking and lung cancer situation in the '50s and '60s where there were relative risks of ten approximately, ten times as high of risk for smokers as for nonsmokers of getting lung cancer, and that was considered a benchmark for strong associations. . . It has subsequently turned out that the level of relative risk for smoking and lung cancer is exceptional among known carcinogens, and that this -- there are not many that have such high relative risks. I'm just giving you a bit of background because the terminology is controversial, and I know it plays into the case of how we -- how we characterize the associations around talc and ovarian cancer . . . . So where you draw the line between strong, moderate, weak, and so on, is a kind of -- is a vague notion.[379]

It is impossible to quote all of the statements from each of the witnesses' testimony and reports that J&J cobbled together and mischaracterized to support its

[378] Moorman Dep at 249:3-14.

[379] Siemiatycki Dep. at 147:2-148:19.

"strength" of association claim. Suffice it to say that the reports and testimony of Drs. Moorman and Siemiatycki cited above are just two examples of the deceptive manner in which J&J has mischaracterized the testimony of the PSC's experts on this issue.

Having largely failed to cause the PSC's expert witnesses to agree and give up a "soundbite" that a 25-45% increased risk qualifies as a "strong" risk, J&J's experts spun selective snippets of the PSC's expert's testimony in a way that would imply that the PSC's experts testified different than they did.[380,381]

J&J's attempt to convert a soundbite or two, taken out of context, into a methodologic flaw is a disservice to the serious causation issue before this Court. J&J's strawman argument is transparent, if not downright misleading and should be rejected.

---

[380] J&J's experts' unfair cherry picking of the PSC's expert reports in an effort to criticize them is in itself an unreliable methodology and demonstrates that they have crossed the line from scientists to litigation advocates. For that reason, among others, the PSC moved to exclude them. *See, PSC's Motion to Exclude Defendants' Epidemiology Experts* at Section IV(D) at 66.

[381] Siemiatycki Dep. at 148:25-149:11 ("Q. So, respectfully, Dr. Siemiatycki, my question was, do you agree with the IARC classification of the increase in risk as, quote, modest? A. So there was no such classification. It was a word used in a sentence, I guess. There is -- they never classified the association as being strong, weak, moderate or whatever. It was part of a narrative about the -- the body of evidence. Do I agree that -- yeah, I would use that term today.").

b. The PSC's experts properly relied on other established cause and effect relationships with risk ratios less than 2.0 to demonstrate that it is reasonable to draw a causal inference from a magnitude of risk that is less than 2.0

To illustrate that causation can be determined from associations reporting a 25%-45% increased risk reported for Talcum Powder Products and ovarian cancer, the PSC's experts noted that there are similar magnitudes of association reported for other exposures that are known to cause disease. J&J would have them ignore that evidence as not relevant.[382]

The PSC's experts described the strength of the association with relationship to other exposures that are also causal. For example, Dr. Moorman wrote:

> The overall associations seen in the talc-ovarian cancer meta-analyses as well as in many of the individual studies are statistically significant, indicating an increased risk of approximately 25-30%. While not as high as other relationships like smoking and lung cancer, these relative risks are in line with other generally accepted causal relationships (e.g. second hand smoke and lung cancer). I consider the strength of association seen in the talc–ovarian cancer epidemiologic studies, to be an important factor in favor of a causal relationship between talc and ovarian cancer, particularly when considered along with the consistency of association seen across these studies.[383]

Similarly, Dr. Siemiatycki wrote:

> [t]he best estimate from the epidemiologic literature is that women who regularly used talcum powder in the genital

[382] Defs.' Mem. at 43-46.

[383] Moorman Rep. at 15.

> area had a 28% higher risk of ovarian cancer than women who did not use such powders. … [T]his RR is in line with many well-recognized risk factors for cancer and other diseases ... Such a high and significant meta-RR could not have occurred by chance. This is a very important factor in how I view the evidence of causality and it supports causality.[384]

An example of this "strength" less than 2.0 evidence is *Table 11* in the Siemiatycki report entitled "**Selected Examples of Some of the Recognized Causal Association that have RR less than 2.0."** He and other PSC experts discuss this type of data for one purpose and for one purpose only--to demonstrate concretely that the strength of association aspect of Bradford-Hill need not exceed 2.0 before a casual association can be reached. That table is reprinted from page 87 of his Report (without references) below:

Agent	**Disease**	**Approximate RR**
Urban air pollution	Lung cancer	1.091
Trichloroethylene	Kidney cancer	1.322
Diesel engine emissions	Lung cancer	1.423
Benzene	Leukemia	1.724
Domestic radon gas	Lung cancer	1.295
Second hand cigarette smoke	Lung cancer	1.64
Intermittent intense sun exposure	Melanoma of the skin	1.616
Estrogen-progestin menopausal therapy	Breast cancer	1.597

[384] Siemiatycki Rep. at 62.

J&J objects to the use of this data as a response to its argument that associations less than 2.0 cannot be found. J&J complains that the PSC's experts have not "conducted a systematic review of the literature" of all of the casual evidence supporting these "causal associations," *i.e.* the nine Bradford Hill aspects for all of these examples.[385] Moreover, J&J protests that the source of the strength for some of these relationships (i.e., HRT) may have come from clinical trials, and not observational studies as are at issue here.[386]

But J&J misses the central point. The PSC's experts are not comparing the nine overall Bradford Hill aspects of *causal* association evidence for each reported association with the nine Bradford Hill aspects that support their views on the *causal* relationship evidence for the talc ovarian cancer association. Nor are they comparing the *source* of the overall data *(i.e.*, the type of study) that supported each association with the *source* of the data supporting the talcum powder ovarian cancer association. They are using the data solely to demonstrate that science recognizes causal inferences where the strength of association is less than 2.0—a conclusion that J&J calls a "methodologic flaw" worthy of wholesale exclusion.[387]

---

[385] Defs.' Mem. at 44.

[386] Defs.' Mem. at 45.

[387] In footnote 82 of its Memorandum, J&J notes, but does not ask, that the Court adopt a 2.0 Relative risk threshold for a causal finding. Not only is that not scientifically supportable, it is not the position of most Courts which have addressed that issue, including in the Third Circuit. *See In re TMI Litigation*, 193 F.3d at 727

2. The PSC's Experts Thoroughly Considered Bias and Confounding When Evaluating Studies as Part of their Analysis of the Totality of the Evidence

As Judge Pisano stated in *Fosamax*, issues of whether experts *properly* considered bias and confounding are not *Daubert* admissibility issues. Rather, they are issues that would affect what weight is to be accorded the evidence to which "defendant is free to address …on cross examination…" *In re Fosamax*, 2013 WL 1558690 at *4; *See also In re Testosterone 2*017 WL 1833173 at *36; *In re Abilify (Aripiprazole) Products Liability Litigation*, 299 F. Supp. 3d at 1325.

a. The PSC's causation experts considered recall bias in the talc studies and like the published literature found it unlikely

Contrary to J&J's argument, the PSC's experts considered whether there was "significant evidence" that the four (4) decades of case-control studies were the subject of "bias" and, like others outside of litigation have observed, they concluded that the risk of bias was minimal (particularly when compared to the real risk of misclassification biases, for example, in the talc cohort studies).[388]

---

n.179; *See also In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1137 (9th Cir. 2002) ("the district court erred in requiring epidemiological evidence which would, like the standard rejected by the Third Circuit in *In re TMI Litigation*, 193 F.3d 613, require a plaintiff to prove exposure to a specific threshold level of radiation that created a relative risk of greater than 2.0."); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1173 (N.D. Cal. 2007) (J. Breyer) (holding that 2.0 issue is not relevant to general causation.

[388]IARC (2010) at 409; Siemiatycki Report at 69 ("There are various potential sources of bias in these studies, some of which could have inflated the true RR

In a further effort to turn what is a difference of opinion on the weight to be accorded to the talcum powder-ovarian cancer studies into facts that the PSC's

---

estimate and some of which would have deflated the true RR estimate. Apart from random measurement error, which is inevitable in such studies and which tends to deflate the RR estimates, there is no certainty that the other potential biases were in fact operative and to what degree. It is my opinion, however, that neither bias nor confounding explains the consistent positive association seen across studies.); McTiernan Report at 63-64 ("Viewed in the context of the high consistency of the study results across time, diverse study populations, and strong study designs, bias and chance as explanation for the increased risk are unlikely."); Kane Report at 9 ("The vast majority of studies and meta-analyses find an association with an increased risk of ovarian cancer. Under these circumstances, viewing the evidence as a whole, the likelihood that the consistent finding of an association can be explained by bias, or chance or confounding is highly unlikely, especially in light of the results of the other lines of evidence."); Moorman Report at 10 ("I considered the potential biases of individual studies, both those that supported and those that did not support an association between talc and ovarian cancer, and how those biases may have impacted the findings. . . . some biases have the potential to lead to an overestimate of the relative risk (e.g. recall bias in case-control studies) while others could result in an underestimate of the relative risk (e.g. incomplete ascertainment of talc use in the cohort studies).); Singh Report at 54 ("Recall bias is less likely to occur for chronic daily exposures such as talc as compared to intermittent short exposures."); Carson Report at 8-9 ("When confounding and bias are exhaustively considered, the positive association remains.") (Taken in their totality, and accounting for sources of bias and differing statistical treatments, these epidemiological studies support a strong association between the perineal use of talcum powder and ovarian cancer."); Carson Dep. at 240:10 to 241:20 ("the same thing can be said about cohort studies. They suffer from other forms of bias, misclassification in particular."); Clarke-Pearson Dep. at 118:13-119:21 ("If your controls are well selected then that negates much of the bias."); Smith-Bindman Report at 34; Smith Report at 16 (Recall and confounding bias in case-control studies appear to have minimal impact.); Wolf Report at 8; Wolf Dep. at 254:5 to 255:12 (" I do agree that one concern of case-control studies is recall bias. I believe that was acknowledged in most, if not all, of the case-control studies and felt not to be an issue. And I looked at that, but the weight of the evidence suggests that most of the studies showed a relationship.")

experts intentionally ignored, J&J posits that "recall bias" was "***in fact***" the source of the ovarian cancer association seen in the case-control studies.[389] In other words, J&J claims that it is a ***fact*** that ovarian cancer "cases" in all case-control studies were differentially prompted by publicity about the Talc-ovarian cancer relationship to recall powder use. Moreover, J&J says that some of the PSC's experts (Siemiatycki and McTiernan) are speculating that studies performed before the first talc ovarian cancer verdict in 2016 did not have a recall bias problem is "pure *ipsie dixit*."[390]

To support this so-called "fact" of recall bias, and the charge that the PSC's experts are "speculating," J&J cites primarily 2 sources; the Schildkraut (2016) study co-authored by the PSC's' expert Dr. Moorman and the *ipsie dixit* litigation opinions of its own experts Diette, Merlo, Ballman and Saenz.

It is truly ironic that J&J would choose to rely on Dr. Moorman's study. In Schildkraut the authors said exactly the <u>opposite</u> of what J&J states about the potential for recall bias in the case-control studies. There, the authors explored whether there was a difference in reporting a relationship to talcum powder use among ovarian cancer cases before 2014 and after 2014 (when publicity surrounding the first ovarian cancer verdict began). After separating data based on the 2014 date, the authors specifically noted that "Our Data ***do not*** support that recall bias alone

[389] Defs.' Mem. at 36.

[390] *Id.*

before 2014 versus 2014 or later would account for the associations with body powder use."[391]

Predictably, Dr. Moorman was asked about recall bias. She testified that this was a specific interest of the Journal editors and, as a result, they explored the issue.[392] She affirmed the talc studies do not support recall bias before 2014:

> I think that probably every meta-analysis published, probably every case-control study that was published, we acknowledge this as a -- recall bias is a potential bias. But I think that we went on to give evidence -- ***I explained why I did not think that it was a complete explanation***. Can we completely rule out any possibility of recall bias? I don't know that we can do it. But I think that as -- for some of the reasons I articulated…. ***And I don't think that we can attribute this association to recall bias***.[393]

And the Schildkraut (2016) study doesn't stand alone in reaching this conclusion. The recall bias that J&J asserts "in fact" explained the association seen in the case-control studies was rejected by others. This would include the *International Agency Research on Cancer* (IARC) in its 2006 talc review which was chaired by the PSC's expert Jack Siemiatycki, Ph.D. As reported in Dr. Siemiatycki's 2008 article following the IARC decision, IARCs epidemiology noted

[391] *Id.* at 1415 (emphasis added)

[392] Moorman Dep. at 239-42.

[393] *Id.* at 241-42.

specifically that pre-2006 talcum case control studies were likely not the subject of recall bias:

> Methodological factors such as recall bias should always be considered in case-control studies. It could have been a problem had there been wide-spread publicity about the possible association between use of body powder and cancer. ***The International Agency for Research on Cancer (IARC) the working group considers that there has not been widespread public concern about this issue and therefore considers it unlikely that such a bias could explain the consistent findings***."[394]

There is one additional fact that supports the PSC's experts' conclusion that recall bias was likely not be a problem with the talcum specific case control studies at issue in the case: ***The association was differentially correlated with serous ovarian cancer (a histologic type) and, if recall bias were a likely source of bias for these studies, it would have effected all subtypes equally***.[395]

---

[394] Langseth 2008 at 358 (emphasis added).

[395] Singh Report at 25 ("While the role of selection and recall bias is a possibility, given higher estimates reported from recent studies, such biases should account for increase in recall for all histologic cancer subtypes and not just serous ovarian cancer."); Kane Report at 23 ("The finding in some studies that serous carcinoma has a stronger association with perineal talc exposure than other histologic subtypes of ovarian cancer also argues against recall bias, as participants are very unlikely to have knowledge about the histologic subtyping of ovarian cancer."); Carson Depo at 240:19 to 241:20 ("you can fault case-control studies for being particularly sensitive to recall bias, but many of these authors who perform these studies indicated that they were well aware of that bias potential and took measures to avoid it."); Smith Report at 16 (Recall and confounding bias in case-control studies appear to have minimal impact.)."); Clarke-Pearson Depo at 164:14-20; Smith-Bindman Report at 17; see also Smith Dep. at 186:23 to 187:22 ("I quoted the part of the paper

The fact that talcum use was differentially associated with some histological subtypes of ovarian cancer and not others strongly supports the PSC's experts' position that recall bias is not the "fact" that J&J, and its litigation experts, say it is. This observation was noted by Health Canada in 2018 which, as noted above, arrived at the same conclusion subsequent to (and independent of) the filing of the PSC's experts' reports in this case:

> In studies where the exposure is simple (e.g., never versus ever use), recall bias is unlikely to be an important source of bias. The positive association is strongest for the serous histologic type (Berge *et al.* 2018; Taher *et al.* 2018); findings that the association may vary by histologic type detracts from the hypothesis of report bias, as the type of bias would likely operate for all histologic types.[396]

As the above examples demonstrate, it was not--and is not--"pure *ipsie dixit*" for the ***PSC's*** experts to have concluded that recall bias was an unlikely source of bias in pre-2014 talc specific case control studies.[397]

---

where the author specifically dressed concerns about recall bias and found them unlikely."); Wolf Report at 8; Wolf Depo at 254:5 to 255:12, 310:18 to 311:20, 313:6 to 313:21 ("In all of the studies, I review the methodology, I look for any evidence of bias, recall bias or anything else. Not every study compared before 2014 and after 2014. This one did, they found no significant difference in recall of use.").

[396] *Health Canada Assessment* at 28.

[397] What is *ipsie dixit*, however, are J&J's expert bias claims, at least those that were used in J&J's Memorandum at 36-37. Apart from relying on the generic "hierarchy of evidence," (which, as demonstrated above, is a methodologic flaw), Drs. Diette and Merlo rely on a handful of articles in the *Chicago Tribune*, *Washington Post* and *San Francisco Chronicle*." *Id* at 37. It is rank speculation that *any* of these articles were read by *any* study participant, particularly in Schildkraut (2016), where the

The PSC's causation experts did not ignore and clearly addressed the potential of recall bias concerns in the talc case control studies. As such, their opinions about what impact alleged recall bias may have as to the significance of the studies presents nothing more than a jury question, and is not a reason to exclude them on *Daubert* methodological reliability grounds. *Compare In re Fosamax*, 2013 WL 1558690 at * 4, *In re Roundup*, 2018 WL 3368534, at *25 (Dr. Portier addressed recall bias and even if it was a close call, the court admitted him), *and In re Testosterone*, 2017 WL 1833173, at *11, *with Zoloft*, 26 F. Supp. 3d at 465 (Dr. Bérard did not "adequately discuss" potential bias and opinion excluded). As described by the Court in *In re Testosterone* and *In re Roundup*, whether the PSC's experts' interpretation is the correct or best explanation is a jury question.

patients were drawn from 11 centers none of which was in the Washington DC Metropolitan area or in California. Nor do J&J's experts begin to explain how recall bias could have affected patients in *other countries* where case-control studies were performed.

b. The PSC's experts properly considered confounding in the talc studies and like the published literature found it unlikely

J&J further asserts that the case control studies may have been flawed because they did not control for potential confounding variables.[398] A potential confounder is a variable that is associated with both exposure and outcome. Failure to control for confounding can lead to spurious results, in that one that may conclude that an association is due to the exposure when in fact, it is due to another variable associated with the exposure – the confounder. As with "recall bias," however, the PSC's experts carefully considered the potential for "confounding" by some unknown variable.[399]

[398] Defs.' Mem. at 38-41.

[399] McTiernan Rep. at 15, 24, 31; Siemiatycki Rep. at 59-60; Moorman Rep. at 28-29 ("Although uncontrolled confounding is a theoretical possibility, to my knowledge, in the more than 30 years of research on talc and ovarian cancer no such confounder has been identified that could account for the increased risk associated with talc use."); Singh Report at 12, 25, 34, 46, 54, 60 (discussing confounding in general and in relation to individual studies); Singh Dep. at 254:5-12; Singh Rep. at 54 ("Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. To invalidate the statistically significant findings of an increased risk of ovarian cancer from the studies, one would have to postulate a degree of selection, recall bias and confounding pervasive across different time periods, different populations which is highly implausible."); Kane Rep. at 9.

As an initial matter, a party does not have to prove that each and every epidemiologic study that they rely on is perfect or that every conceivable confounding variable has been identified and controlled for. As the courts in *In re Roundup* and *In re Abilify* recently observed:

> Reliable epidemiological studies should account for confounders where they are identified, although "failure to control for every conceivable potential confounder does not necessarily render the results of an epidemiological study unreliable.[400]

With respect to the case control studies, the theoretical issue of a failure to control for confounders is exceedingly small for several reasons.

First, this case does not rest on the interpretation of a single study or even a handful of studies. There are literally dozens of tac studies spanning 40 years and as Dr. Moorman observed: "To my knowledge, in the more than 30 years of research on talc and ovarian cancer no such confounder has been identified that could account for the increased risk associated with talc use."[401] This fact has been noted by other scientists as well.[402]

---

[400] *In re Roundup*, 2018 WL 3368534 at *8 (quoting *In re Abilify*, 299 F. Supp. 3d at 1322).

[401] Moorman Rep at 28-8.

[402] *See e.g.* Narod, 2016 at 2 ("It is unlikely that the association between talc and ovarian cancer is due to confounding and so it is fair to say that if there is a statistically robust relationship between talc use and ovarian cancer it is likely to be causal (albeit with intermediate factors such as inflammation); Cramer, 1999 at 356:

Second, while not every talc study adjusted for every one of J&J's theoretic variables (family history of cancer, menopausal status, BMI, contraceptive use and douching), some did and the overall risk ratio was consistent across studies. This, of course, indicates that the theoretic confounders J&J has speculated on were not *real* confounders.[403]

Against this backdrop, J&J has now come-up with a new confounder to explain the increased risk based on Gonzalez (2016): douching. Using this variable, talc is the exposure, ovarian cancer is the outcome, and douching is the potential confounder. J&J argues that most studies examining Talcum Powder's association with ovarian cancer failed to control for douching as an uncontrolled confounder. They speculate that the increased risk of ovarian cancer seen with genital Talcum Powder use may have been due to talc users being more likely to also use douching products.

The PSC's experts are accused of dismissing douching as a potential confounder. Dr. Moorman, in particular, is accused of ignoring this potential

---

("In summary, we have demonstrated a consistent association between talc and ovarian cancer that appears unlikely to be explained by recall or confounding.")

[403] *See, e.g.,* Siemiatycki Report at 59 ("Given that the main studies have controlled for the main risk factors, I consider it unlikely that this operates. . . . while there is some variability between studies in the list of covariates, the main known potential confounders (age, BMI or weight, parity) have been controlled for in almost all studies.").

confounder.[404] To the contrary, Dr. Moorman acknowledges that vaginal douching, associated with ovarian cancer risk was examined as a potential confounder in Gonzalez (2016).[405] While the data from Gonzalez suggests douching may be a potential confounder, the analysis they performed revealed empirical evidence that adjusting for douching using statistical modelling had a negligible effect on the association between Talcum Powder use and ovarian cancer, indicating that the association between Talcum Powder use and ovarian cancer was not confounded by douching.[406] It is Dr. Moorman's opinion that if douching was a confounder of the association between talc use and ovarian cancer, one would have expected a substantial change in the hazard ratio once they adjusted for douching - this was not demonstrated.[407]

Third, and perhaps most important, one additional factor must be considered—one which neither J&J nor its experts even try to explain. That is that in order for confounding to be the explanation for the risk seen between the use of talc and ovarian cancer, the unknown theoretic variable would have to have been a

[404] Defs.' Mem. at 38.

[405] Moorman Rep. at 28.

[406] *Id*.

[407] Affidavit of Patricia Gripka Moorman, M.S.P.H., Ph.D., dated May 21, 2018 at 3, 4 (discussing Hartge *et al.* (1983) and Harlow *et al.* (1992), which ruled out douching as a likely confounder), attached as **Exhibit 151**.

very large risk in and of itself and one that would have had to have gone undetected for decades. This fact was explained almost 20 years ago when J&J and the talc industry submitted an "expert report" by Dr. Kenneth Rothman to the National Toxicology Program (NTP) in support of its position that talc is not a human carcinogen.[408] In his 2000 report, Dr. Rothman was quite clear that confounding variables that J&J discusses (family history, BMI, reproductive status and contraceptive use) were ***not a likely explanation*** of a relative risk in the range of 1.31:

> **Confounding**
>
> Although there are some strong risk factors for ovarian cancer, for any of them to be confounding to an extent that could account for the positive relations that have been reported [and overall relative risk of 1.31], they would have to be strongly correlated with talc use. ***Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association.*** Of course, it remains possible that yet unidentified risk factors for ovarian cancer could be important confounders, and several such factors in the aggregate could give risk to an overall association as weak as the one between talc and ovarian cancer.[409]

[408] The NTP did not reach a conclusion one way or another. It deferred that decision and has not taken the issue up again. 70 Fed. Reg. 60548, 60553, attached as **Exhibit 152**.

[409] Rothman, *et al., Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer* (2000) at 5.

The truth is that in the past 40 years of trying, J&J has failed to identify a confounding variable which could even theoretically account for the increased relative risk. That includes douching.

As Judge Pisano noted in *Fosamax*, however, the extent to which an expert failed to consider or address a confounding, affects the weight and not admissibility of the expert's testimony and "Defendant is free to address these issues on cross examination…"[410]

E. THE PSC'S EXPERTS MAY RELIABLY OPINE THAT THE "DOSE RESPONSE" ASPECT OF THE BRADFORD HILL CAUSATION GUIDELINES ARE MET WHERE THERE IS EVIDENCE OF DOSE RESPONSE FROM THE TALC OVARIAN CANCER OBSERVATIONAL STUDIES

J&J argues that the PSC's experts' testimony on dose response, another Bradford Hill aspect, is unreliable and must be excluded.[411]

In support of their Bradford Hill causation analysis, the PSC's experts opine that there is evidence of a dose response relationship seen in the subset of observational studies that actually looked for it.[412] In particular, they note that there

[410] *In re Fosamax*, 2013 WL 1558690 at *4

[411] Defs.' Mem. at 67-78.

[412] Chang (1997); Cramer (2016); Gates (2008); Harlow (1992); Rosenblatt (1992); Schildkraut (2016); Wu (2009); Terry (2013).

are studies that looked at cumulative dose (frequency) over time (duration).[413] In other words, there is evidence that the *more* applications of talcum powder the greater the risk. While most of the evidence was in the form of trends seen on the data and reported in the relevant studies, one meta-analysis of *all* talc studies, a 2018 meta-analysis by Berge (2018) found "*a weak but statistically significant association between genital use and ovarian cancer, which appears to be limited to serous carcinoma with a suggestion of dose response.*"[414] Similarly, the Penninkilampi

[413] Kane Report at 35 ("Yet, when studies have evaluated duration and frequency of perineal talc use, most have found an increased risk of ovarian cancer with increased exposure[.]); Moorman Report at 30-31 ("When considering the studies that examined dose-response associations considering both dose and frequency to estimate the total number of applications of talc, the majority did find significant trends of higher risk with more lifetime applications of talc."); see also Carson Report at 9; Wolf Report at 15; Siemiatycki Report at 63; McTiernan Report at 42; Plunkett Report at 7-8, 47-48, 50, 52; Carson Report at 9; Carson Dep. at 255:3-23 ("Although some studies have failed to find evidence of a dose-response relationship, several more recent reports have shown a clear dose-response when the number of subjects rose to a level producing sufficient statistical power to allow the analysis after subdivision of subjects into pertinent categorical groups, and frequency and duration were measured"); Clarke-Pearson Dep. at 159:11-16, 192:1-2 ("There is dose response evidence. It's not in every single study, but we are aware of dose response."); Smith-Bindman Report at 25, 28, 39-40; Smith-Bindman Dep. at 366:3-367:12 ("In summary, most but not all studies of talcum powder products and ovarian cancer show a dose response."); Smith Report at 20 ("this refers to dose response relationship which is not seen in all of the epidemiologic studies, but is demonstrated in some.'); Wolf Report at 15; ("Many of the studies did not obtain the necessary information to evaluate dose response and lacked adequate power to assess dose-response accurately. Despite the lack of sufficient information in many studies, recent meta-analyses/pooled study and a case-control studies do show a dose response, using frequency and duration of use as parameters.")

[414] Berge (2018) at 248.

(2018) meta-analysis found a higher risk with more than 3,600 lifetime applications versus those with fewer than 3,600 lifetime applications.[415]

J&J argues that this type evidence and these observations are simply not enough to consider in a Bradford Hill analysis and that the PSC's experts applied an improper methodology for even considering it.[416] As set forth below, J&J is wrong as a matter of both science and the law. *See, e.g*, *Roundup*, 2018 WL 3368534, p *21.

1. J&J Misstates and Then Misapplies the Scientific Standard for "Dose Response" for a Bradford-Hill Analysis

J&J insists that the *evidence* is insufficient for the PSC's experts to consider as part of their Bradford-Hill dose response analysis. As J&J must admit, however, there is dose response evidence and a clear dose response trend.[417] J&J's contention therefore is that the evidence is *not enough* for the PSC's experts to discuss the issue.

J&J's argument about "dose response" boils down to the definition of dose response in the context of the Bradford-Hill framework and the threshold that must be met before an expert can rely on it. On the one hand, the PSC (and their experts) contend that scientists performing a Bradford-Hill analysis look for and consider *any*

[415] Penninkilampi (2018) at 44.

[416] Defs.' Mem. at 67-78.

[417] Defs.' Mem at 67.

evidence of dose response. On the other hand, J&J (and its experts) argue the existence of any *evidence* of a dose-response is not enough, as the dose response evidence must be clear and seen consistently *"through the body of data,"*[418] and must be "statistically significant"[419] As the Court is aware, the PSC has filed a *Motion to Exclude Defendants' Epidemiology Experts*[420] because they adhered to this higher, unsupported and incorrect standard.[421]

In order for this Court to address J&J's argument on this issue, the Court must discern what is meant by "dose response," not generally, *but in the context of a Bradford-Hill analysis*. In this regard, and as a starting place, it is important to consider what Sir Bradford Hill *actually* said about this aspect:

> Biologic Gradient*:* Fifthly, if the association is one which can reveal a biologic gradient, or dose response curve, then

---

[418] *Id.*

[419] Defs.' Mem. at 73, n. 167.

[420] *See generally PSC's Motion to Exclude Defendants' Epidemiology Experts* at 50-57.

[421] By way of example, Dr. Ballman, J&J's statistician expert claimed that there was an exceedingly high threshold for dose response, though she notably provided no support for her assertion:

> To establish a dose-response relationship [to evaluate the talc ovarian cancer relationship], the **necessary evidence** is increasing risk with increasing dose, **statistical significance** and **consistency**. Consistency in this context includes **repeated demonstration of the result across different studies, including different study designs, and different measures of dose.**

Ballman Rep. at 29 (emphasis added); s*ee also id.* at 19.

> we should look most carefully for such evidence… [With respect to dust], [t]he dustier the environment the greater the incidence of disease we would expect to see. **Often the difficulty is to secure satisfactory quantitative measure of the environment which will permit us to explore this dose response. But we should invariably seek it.**[422]

It is therefore a fundamental tenet of epidemiology that dose response *evidence* -- much less the "consistent" and "statistically significant" and "clear" evidence J&J urges -- is not a *sine qua non* for a reliable causal inference supported by other Bradford Hill criteria. That fact is explained in basic epidemiology textbooks, including ones used and authored at J&J's experts' institutions.[423]

Despite J&J's assertions, dose-response is not an essential feature for assessing causation *under the Bradford-Hill guidelines*. As the *Reference Manual* establishes, dose-response evidence under Bradford-Hill is simply one factor in a causal assessment and it is "not essential."[424] And, where the evidence is based on epidemiology, "good evidence to support or refute the threshold-dose hypothesis is

---

[422] Hill at 298 (emphasis added).

[423] Gordis, *Epidemiology* at 251 ("absence of a dose-response relationship does not necessarily rule out a causal relationship"); Rothman, *et al.*, *Modern Epidemiology* at 28 (". . . the existence of a monotonic relationship is neither necessary nor sufficient for a causal relationship."); Oleckno, *Epidemiology: Concepts and Method*s at 189 ("The absence of a dose response relationship does not necessarily mean that the association is non-causal however. … Once again, several guidelines should be considered in assessing causation.").

[424] *Ref. Man.* at 603

exceedingly unlikely because of the inability of epidemiology or animal toxicology to ascertain very small effects."[425]

For that reason, numerous courts in drug product liability cases have not defined dose response in the way J&J and its experts do in this case, *i.e.* "Statistically significant" and "consistent" across studies. *McClain* states that "[o]ne should not conclude . . . that to pass *Daubert* muster an expert must give precise numbers about a dose-response relationship. Some ambiguity about individual responses is expected." *McClain*, 401 F.3d at 1241 n.6.[426]

From Professor Hill's own description of this dose response consideration of his causal analysis framework to the case law interpreting it, it is apparent that the real question –and the read definition of dose response--is not whether there is

[425] *Id.* at n. 160.

[426] *See also, e.g., In re Neurontin,* 612 F. Supp. 2d 116 (denying motion to exclude plaintiffs' general causation experts' opinion that Neurontin can increase risk of suicide without determination of dose-response relationship); *In re Fosamax Prod. Liab. Litig.*, 645 F. Supp. 2d 164 (S.D.N.Y. 2009) (denying motion to exclude plaintiffs' general causation experts' opinion that drug can cause osteonecrosis of the jaw without requiring demonstration of toxic dose); *Bartlett v. Mut. Pharm. Co.*, 759 F. Supp. 2d 171 (D.N.H. 2010) (denying motion for judgment as a matter of law because plaintiff presented sufficient evidence that drug's risks outweighed its benefits without discussion of toxic dose); *In re: Zicam Cold Remedy Mktg., Sales Practices, & Prod. Liab. Litig.*, 797 F. Supp. 2d 940, 945–946 (D. Ariz. 2011) ("Plaintiffs need not provide precise information concerning the exposure necessary to cause specific harm to humans... A qualitative, rather than quantitative, analysis can suffice."); *In re Avandia*, 2011 WL 13576 (denying motion to exclude plaintiffs' general causation experts' opinion about causal connection between Avandia and myocardial infarction without discussion of toxic dose).

absolute proof of dose response. Rather, the question is: **Is there *any* evidence of *any* kind which would support a dose-response relationship?** If so, that evidence would support a causal inference under the "biologic gradient" aspect of Hill's Framework.[427] If not, other Hill aspects should be considered since "the absence of a dose response relationship does not necessarily rule out a causal relationship."[428,429]

2. There is Evidence of a Dose-Response Relationship between Talcum Powder Exposure and Ovarian Cancer

It is not surprising that in this Talcum Powder ovarian cancer case, where the dose response is based primarily on observational data, that the high bar of evidence that J&J would demand would not be available. Both Professor Hill and the *Reference Manual* recognize that it would be both "difficult…to secure" and "exceedingly unlikely" to obtain. That being the case, epidemiologists applying the multiple aspects of Bradford-Hill look for any evidence of it, not just "clear" evidence of it.

In this case, there is "evidence" of a positive dose response for experts to consider among all of the other Bradford Hill aspects.[430] This is true even as the

---

[427] *See Tylenol, supra.*

[428] Gordis, *Epidemiology* at 251.

[429] *See In re Avandia*, 2011 WL 13576 at *14 (determining expert's Bradford Hill analysis was reliable despite the expert being unable to assess a dose response).

[430] Siemiatycki Dep. at 122:22-123:7 ("My view is that the data are certainly compatible with the notion of a dose-response relationship. It – it trends in that direction of that conclusion. It's not definitive yet. It's not definitive. But I believe

PSC's experts freely admit that the dose response data from the observational studies are not unequivocal and might require additional research.[431]

Dose-response data from the following studies which support the presence of a dose-response relationship between use of Talcum Powder Products and ovarian cancer:

- **Penninkilampi (2018) at 45** (the study results revealed "a slightly greater increase risk of ovarian cancer with > 3600 lifetime applications compared with those with < 3600 lifetime applications. The number of lifetime applications is a more valid measure of the patient's exposure to perineal talc than either duration or frequency of use alone.)

- **Berge (2018) at 1** ("This metanalysis resulted in a weak but statistically significant association between genital use of talc and ovarian cancer…with a suggestion of a dose-response.");

- **Schildkraut (2016) at 1413, 1414** (the study results, based on two lifetime cumulative dose categories (< 3600 and >3600 applications revealed point estimates of 1.16 and 1.67 respectively and are evidence of a dose- response. The test for trend was significant for only "any" genital powder use (Table 2).

- **Cramer (2016) at 337, 345** ("An OR of 1.49 (95% CI – 1.06, 2.10) was associated with more than 20 talc-years (>7,200 applications) and a dose response. "Overall, there is an association between

---

the bulk of the evidence, especially from the Terry study and partly from, I think it's the, Schildkraut study, which are the most powerful ones for that question, but certainly the Terry study is by far the most important one, does tend to indicate dose-response relationship."); McTiernan Dep. 200:5-8 ("The data to me show that there is an increased risk of ovarian cancer with use of talcum powder products, and I think their data show it very clearly, and they have shown dose response relationships as well.").

[431] Defs.' Mem. at 67, n 160.

genital talc use and EOC and a significant trend with increasing 'talc-years" of use.");

- **Terry (2013) at 6** ("Alternatively, the association between genital-powder exposure and ovarian cancer risk may not be linear and modest exposure may be sufficient to increase cancer risk.");

- **Wu (2009) at 1** ("Risk of ovarian cancer increased significantly with increasing frequency and duration of talc use…"; "Our study adds to the small group of studies that have investigated the combination of frequency and duration of talc use on ovarian cancer risk.");

- **Whittemore (1988)** (observing a positive dose response relationship with frequency of exposure); and,

- **Rosenblatt (1992)** (positive association (RR=2.35) for exposure longer than median length of time of enrollees).

J&J continues to misrepresent the Terry (2013) findings suggesting that the Terry Study found "***no dose-response relationship.***"[432] To be clear, when looking at the Terry (2013) results, which assembled data from 8 teams and 10 studies the results demonstrate evidence of a dose-response relationship.[433] Again the absence of statistical significance of a trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response. Moreover, constructing this argument, demonstrates that J&J lacks an understanding of statistical trend analyses. J&J admits that there is a "significant dose trend reported in the data from Terry

[432] Defs.' Mem. at 71.

[433] Terry (2013 at 819 Table 5).

2013 when non-users are included in the comparison."[434] It is simply incorrect for J&J to conclude that it is inappropriate to include the unexposed category as part of the study results when examining subject in different "dose "categories. Reliance upon dose response calculations that include non-exposed groups is accepted methodologic practice in epidemiology.[435] In Terry (2013), the authors employed appropriate methodology in assessing dose-response effects. They correctly categorized participants who had used genital powder into 4 groups by lowest to highest level of use (quartiles), and compared their risk for ovarian cancer to that in non-users. In so doing the study authors found a statistically significant increase in risk with an increasing number of genital powder application for non-mucinous epithelial ovarian cancer when non -users were included in the analysis.[436]

---

[434] Defs.' Mem. at 73.

[435] *See generally* Ludwig Hothorn, *et al.*, *Trend Tests for the Evaluation of Exposure-Response Relationships in Epidemiological Exposure Studies*, 6 Epidemiologic Perspectives & Innovations 1 (2009), attached as **Exhibit 153**; Sander Greenland, (1995), *Dose-Response and Trend Analysis in Epidemiology: Alternatives to Categorical Analysis Epidemiology*, 6 Epidemiology 356-365 (1995), attached as **Exhibit 154**.

[436] Terry (2013) at 817-819; *see also* Siemiatycki Dep. at 122:22-123:7. ("My view is that the data are certainly compatible with the notion of a dose-response relationship. It – it trends in that direction of that conclusion. It's not definitive yet. It's not definitive. But I believe the bulk of the evidence, especially from the Terry study and partly from, I think it's the, Schildkraut study, which are the most powerful ones for that question, but certainly the Terry study is by far the most important one, does tend to indicate dose-response relationship.")

J&J posits that the PSC's experts employed an unverifiable made-for-litigation analysis that does not comport with a Bradford-Hill analysis. However, this is not so. This evidence of dose response for talcum powder and ovarian cancer observed by the PSC's experts has also been observed by other scientists *outside* of the litigation context. For example, in analyzing the "dose response" aspect of Bradford Hill, Taher (2018) observed:

> Of the 12 studies reporting a positive association, six studies found significant exposure-response trend, particularly with medium and high frequency groups. Regarding duration/exposure to talc, severely studies reported the greatest risk 20+ years of use exposure, followed by the 10-20 years group, then the < 10 years group.[437]

In *In re Roundup*, the court addressed the admissibility of similar dose response data. There, as here, there was less than unequivocal evidence of dose response.[438] Yet, the court properly concluded that this was a jury question and <u>not</u> one that required exclusion under *Daubert*:

> Although the better conclusion might be that these data are inconclusive, Dr. Portier's assessment that the biological gradient criterion is moderately supportive of a causal association does not constitute an unsupported scientific leap.[439]

---

[437] Taher (2018) at 26.

[438] *In re Roundup*, 2018 WL 3368534, at *21 ("some of the data from the case control studies support Dr. Portieres conclusion but others do not as he acknowledged.").

[439] *Id.* (citation omitted).

The PSC's experts applied a reliable methodology in relying on the very type of "dose response" evidence that Professor Hill anticipated. Any weaknesses in this evidence go to weight, not admissibility.[440]

F. THE PSC'S EXPERTS MAY RELIABLY OPINE THAT "BIOLOGIC PLAUSIBILITY" EXISTS WHERE THERE ARE MULTIPLE LINES OF EVIDENCE SUPPORTING THE PLAUSIBILITY THAT TALCUM POWDER PRODUCTS CAUSE OVARIAN CANCER

Although plaintiffs are not required to prove mechanism of action (how an exposure causes a disease or injury),[441] such evidence where available, can be very important. The PSC's causation experts have opined that multiple lines of non-epidemiologic, mechanistic, biologic and geologic evidence (hereinafter "biologic evidence") is consistent with, and indeed fully supportive of, the conclusion that the epidemiologic *association* observed between Talcum Powder Products and ovarian cancer is a *causal* one. The biologic evidence that the PSC's experts rely on is not "weak" and has not been invented for this litigation as J&J contends in its *Biological Plausibility Motion*.[442] To the contrary, the biologic plausibility of this causal

---

[440] *In re Roundup, supra*.

[441] *See Section IV(F)(1), infra.*

[442] *See* J&J's Memorandum of Law in Support of Motion to Exclude Plaintiffs' Experts Opinions Related to Biologic Plausibility (ECF No. 9736-1) at pages 78-82 ("*Biological Plausibility Motion*"). The PSC is filing a separate response to J&J's Biological Plausibility Motion, concurrently which is incorporated herein as if set forth in its entirety.

association has long been noted in the published epidemiologic, gynecologic and oncologic literature and textbooks and, further, has been reiterated by regulatory bodies (including the FDA and Health Canada).

The PSC's experts have properly considered the following biologic evidence which supports their opinions that Talcum Powder Products is capable of causing ovarian cancer because: (1) talcum powder is capable of reaching the fallopian tubes and ovaries either through migration from the perineum or through inhalation; (2) once there, talcum powder causes chronic inflammation and oxidative stress, which increases the risk of epithelial ovarian cancer through a well-described cascade of biological and molecular processes involving inflammation and oxidative stress; and, (3) J&J's Talcum Powder Products have been shown to contain multiple carcinogens and suspected carcinogens, including asbestos, fibrous talc, nickel, chromium, cobalt, and certain fragrance chemicals.

1. J&J Misstates and Then Misapplies the Biologic Plausibility Standard for "Biologic Plausibility," Which Does Not Mean Biologic Certainty

Before addressing the evidence favoring biologic plausibility in this case, the Court must consider what is meant by the term "biologic plausibility."

In virtually every case where a plaintiff alleges that an exposure causes a disease, the defendant attempts to challenge the reliability of the plaintiff's expert opinion by improperly redefining biologic plausibility under Bradford-Hill, from

biologic *plausibility* to biologic *certainty*. J&J does so here, arguing that that the mechanism by which Talcum Powder Products are capable of causing ovarian cancer must be certain, or reasonably so, to allow expert testimony on general causation.[443] The erroneous heightened standard is contradicted by the scientific literature and in the case-law interpreting it.

The starting place for the correct definition of "biologic plausibility" must begin with what Professor Hill actually said on the subject. In his 1965 article, Hill stated that:

> *It* will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced that we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.[444]

The concept of "plausibility" has not changed since Professor Hill described it. For example, in a textbook relied on by J&J's expert Dr. Merlo, Olekno W.A, Epidemiology: Concepts and Methods (2008), Professor Oleckno writes:

> **Biological Plausibility:** The basic question here is, does the association make biological sense? Is the association credible based on our understanding of the natural history of the disease or possible pathogenic mechanisms?[445]

[443] Defs.' Mem. at 79.

[444] Hill (1965) at 298.

[445] Oleckno (2008) at 189.

Moreover, Professor Rothman made the same point in his textbook *Modern Epidemiology:* "In asking whether [an association] is causal or not, one of the considerations to take into account is its plausibility . . . [n]evertheless, no approach can transform plausibility into an objective causal criterion."[446]

Courts have repeatedly rejected attempts to redefine biologic plausibility as J&J and its retained experts attempt to do in this case.[447] For example, in *In re Abilify*, the court summarily rejected a defendants' contention that plausibility meant certainty or, in J&J's words "reasonable certainty":

> At this point, the Court finds it important to emphasize that determining whether an expert's opinion is "biologically plausible" is a far different inquiry than determining whether an opinion is "biologically certain." *See, Daubert*, 509 U.S at 590 [] (It would be unreasonable to conclude that the subject of scientific testimony must be "known "to a certainty; arguably there is no certainty in science.").[448]

Similarly, in *In re Testosterone*, the defendant AbbVie argued, as J&J does here, that the plaintiffs would have to demonstrate that there was specific biologic evidence linking the specific product to the particular disease before "plausibility"

---

[446] *Rothman* (2009) at 28-29.

[447] Because J&J's epidemiologist have used a "biologically plausibility" standard to evaluate the evidence that is more in keeping in keeping with J&J's legal theories and not the scientific definition, the PSC moved to exclude their testimony as unreliable. *See PSC's Motion to Exclude Defendants' Epidemiologists* at 57-62.

[448] *In re Abilify*, 299 F. Supp. 3d at 1308.

is met under a Bradford Hill analysis. There the court could not have been clearer that this is not the standard:

> AbbVie's primary criticism of plaintiffs' experts' mechanism theories is that the experts do not rely on any studies that demonstrate a link between use of TRT in human beings and the proposed mechanism plus a link between the proposed mechanisms to cardiovascular events. ***But AbbVie cites to no authority that says experts must be held to so high a standard in demonstrating the plausibility of mechanism. Rather, an analysis of biological plausibility "asks whether the hypothesized causal link is credible in light of what is known from science and medicine about the human body and the potentially offending agent.***

In re Testosterone, 2017 WL 1833173, at *11 *citing Milward v. Acuity Specialty Prod. Grp., Inc.*, 639 F.3d 11, 23, 26 (1st Cir. 2011). *See also*, *In re Fosamax,at *6* ("testimony to be admissible, [he] is not required to show that a mechanism has been definitely established.")

Indeed, the *Reference Manual* itself makes clear that even an observation is "inconsistent with current biological knowledge, it should not be discarded, but the observation should be confirmed before significance is attached to it."[449] This strong admonition against equating biologic *plausibility* with biologic *certainty* is particularly true when performing a Bradford Hill causation analysis in which plausibility is only a *part* of their overall analysis. This point was made by in *In Re*

[449] *Ref. Manual* at 604-5.

Roundup. There, the court considered the testimony of an epidemiologist who testified that there were biologically plausible mechanisms whereby glyphosate could cause *against the backdrop of observational data*.[450] Though that expert was likely not qualified to testify "the toxicology evidence in any detail," her testimony about biologic plausibility was still admissible as part of her overall Bradford Hill analysis:

> [T]o the extent she simply opines that, as an epidemiologist engaging in a Bradford Hill analysis, a review of the published mechanistic literature suggested it was biologically plausible that glyphosate could cause NHL in humans, that limited conclusion is admissible. *Cf.* Rothman at 28-29. With her Bradford Hill analysis cabined in this way, Dr. Ritz's opinion that glyphosate causes NHL, and has caused NHL in those who have used it in the manner studied, is admissible.[451]

Clearly, J&J and its experts have asked this Court to adopt a definition of "biologic plausibility" that is inconsistent and more stringent than that envisioned by either science or the cases that interpret it. This approach should be rejected.

[450] *In re Roundup*, 2018 WL 3368534, at *27.

[451] *Id.*

2. The PSC's Experts Have Reasonably Relied on Three Broad Areas of Biologic Evidence Consistent with the Association between Talc and Ovarian Cancer being a Causal Association

a. It is biologically plausible that Talcum Powder Products (and its constituents) reach the ovaries either through migration or inhalation

In order to cause ovarian cancer, J&J's Talcum Powder Products must reach the ovaries. There is, in fact, credible evidence in the literature that Talcum Powder reaches the ovaries by migration through the genital tract or by inhalation (or both).

Outside of litigation, government agencies and their employees have noted that both migration and inhalation are *plausible* exposure mechanisms by which Talcum Powder Products can be carried to the ovaries. For example:

- **FDA Letter 2014: "**the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable. It is, therefore, plausible that perineal talc (and other particulate) that reaches the endometrial cavity, Fallopian Tubes, ovaries and peritoneum…"[452]

- **Health Canada Screening Assessment (2018):** "Talc particles have been observed and detected in the ovaries of humans (Heller *et al.* 1996a, 1996b), and perineal exposure to talc has also been associated with a presence of talc in lymph nodes and ovaries of women diagnosed with ovarian cancer (Heller *et al.* 1996; Cramer *et al.* 2007). Migration of talc particles from the vagina to the ovaries has been identified as a plausible explanation of these findings (Henderson *et al.* 1986), and retrograde movement of talc particles in humans through the reproductive tract to the ovaries has been suggested (Heller *et al.* 1996; Cramer *et al.* 2007). Inert particles with the same size as talc (5 to 40 μm in diameter) and placed in the

[452] Musser Letter at 5.

vagina can be transported to the upper genital tract (Egli and Newton 1961; De Boer 1972; Venter and Iturralde 1979)."[453]

- **IARC (2010):** Regarding exposure of the general population, "Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powders) are the primary routes of exposure." [454]

Consistent with these biologic observations made outside litigation, the PSC's experts agree with these observations that there is credible biological evidence that Talcum Powder reaches the ovaries.[455] That evidence is consistent with their conclusion that the association seen in the epidemiologic studies is a causal association and is outlines in the Factual Background Section of this brief, *supra* at *Section III.* In assessing biologic plausibility prong of Bradford Hill, the PSC's experts were using a proper methodology for relying on talc's ability to reach the ovary through migration or inhalation.

[453] Health Canada Assessment at 9.

[454] IARC (2010) at 232.

[455] Plunkett Report at 28-38; Kane Report at 14, 35; McTiernan Report at 58-59; Moorman Report at 33; Siemiatycki Report at 30, 65; Smith-Bindman Report at 35; Carson Report at 8; Clarke-Pearson Report at 7-8; Smith Report at 16-17; Wolf Report at 10-11.

b. It is biologically plausible that talcum powder products (and its constituents) cause both inflammation and oxidative stress, known mediators of cancer

In order to cause ovarian cancer, J&J's Talcum Powder Products (including all of its constituents) should also provoke a response consistent with carcinogenesis. There is, in fact, credible evidence that Talcum Powder Products (and its constituents) can provoke an inflammatory response and induced oxidative stress. Both inflammation and oxidative stress are widely accepted mediators of cancer.[456] As both epidemiologists and regulatory agencies, including the FDA, have noted, both of these mechanisms provide credible plausible explanations for how Talcum Powder Products and its constituents are capable of causing ovarian cancer. For example, Health Canada recently observed that:

> With respect to talc specifically, local irritation leading to an inflammatory response is one of the possible mechanisms of tumor progression that is frequently hypothesized. There is support for an association of inflammation and increased risk of ovarian cancer.[457]

[456] Plunkett Rep. at 46 ("When considered together, the scientific literature on the biological effects of talc, as well as asbestos and other constituents routinely found in talc (discussed above), provide sufficient evidence to show that these chemicals produce cellular changes that have been linked to carcinogenesis and that the biological mechanism for carcinogenesis (ovarian and/or lung) following exposure to talcum powder products likely involves induction of a chronic inflammatory response."); Moorman Rep. at 34; Kane Rep. at 10-13, 35; McTiernan Rep. at 59-60; Siemiatycki Rep. at 65; Singh Rep. at 58-59; Smith-Bindman Rep. at 15; Wolf Rep. at 15; Carson Rep. at 10; Clarke-Pearson Rep. at 4; Smith Rep. at 17-18; see also Plunkett Dep. at 128:4- 19,189:11-193:25; *see also* Fletcher, *et al.* (2019).

[457] Health Canada Assessment at 18.

That talc and its constituents can cause inflammation and oxidative stress consistent with the mediation of cancer is outlined in of this brief, *supra* at *Section III(A)(2)(b).* The PSC's experts properly relied on this data as adding to the biologic plausibility of talc causing ovarian cancer.

c. It is biologically plausible that Talcum Powder products are capable of causing ovarian cancer because they contain known carcinogens like asbestos, fibrous talc and heavy metals and other carcinogenic chemicals[458]

The PSC's experts have relied on the credible evidence that J&J's Talcum Powder Products contain--and have contained known or probable carcinogen--to support their opinion that it is biologically plausible that Talcum Powder Products are capable of causing and ovarian cancer. This evidence includes: 1) Published literature 2) Contemporaneous positive testing of the talc used in J&J's Talcum Powder Products; 3) The testing by Dr. Longo and Rigler. These carcinogens include asbestos, fibrous talc, nickel, chromium and cobalt.

Prior to this MDL, J&J and its consultants admitted that the presence of known or suspected carcinogens in its Talcum Powder Products would present a

[458] The PSC incorporates herein its Responses and Oppositions to J&J's Memorandum of Law in Support of Motion to Exclude Plaintiffs' Experts' Asbestos-Related Opinions and J&J's Memorandum of Law in Support of Motion to Exclude Plaintiffs' Experts' Opinions Regarding Alleged Heavy Metals and Fragrances in Johnson's Baby Powder and Shower to Shower, both being filed contemporaneously with this brief.

biologically plausible explanation for the association between its products and ovarian cancer. Perhaps most revealing are the published admissions of J&J's prior external consultants who also became litigation experts, Michael Huncharek MD and Joshua Muscat, Ph.D. Not only did Drs. Huncharek and Muscat *publish* their views on asbestos contaminated Talcum Powder and biologic plausibility, they submitted their views to FDA in a report endorsed by the Talc Industry (including J&J and PCPC). They published that report in a commentary, Huncharek (2011).[459] Notably, J&J has now abandoned them as litigation experts, likely because of the admissions they made about Talcum Powder contaminated with asbestos.

In Huncharek (2011), these J&J consultants were predictably critical of the epidemiologic evidence linking pure talc to ovarian cancer. However, in doing their analysis of the composition of Talcum Powder Products, they published an admission that is critical now: the presence of asbestos (or presumably other carcinogens) would change the causal calculus and would provide a credible biologically plausible explanation for the epidemiologic literature reporting an association between Talcum Powder Products and ovarian cancer. In that article, they stated that:

[459] Michael Huncharek & Joshua Muscat, *Perineal Talc Use and Ovarian Cancer Risk: a Case Study of Scientific Standards in Environmental Epidemiology*, 20 Eur. J. Cancer Prevention 501 (2011), attached as **Exhibit 155**.

> **Clearly, [talcum powder] products could possibly represent a carcinogenic risk secondary to the asbestos contamination**. It should be pointed out that this in no way implicates talc as a toxin as **the problematic constituent of such products was the asbestos fibers, not talc**.[460]

That was not the only time that this concession was made. Indeed, Drs. Huncharek and Muscat made the point even more emphatically in another 2007 article also supported by J&J and the Talcum Powder industry:

> If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogenic effect as it contains a known carcinogen.[461]

The PSC's experts properly rely on evidence of contamination of J&J's Talcum Powder Products with known or probable carcinogens provide as a credible biologic explanation for ovarian cancer.[462] Indeed, IARC has declared that *both*

---

[460] Huncharek (2011) at 506; *see also* July 21, 2009 *Comments on: Citizens Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products* submitted by Personal Care Products Council, attached as **Exhibit 156**; Deposition of Joshua Muscat, October 25, 2018 ("Muscat Dep.") at 525:20-529:16, attached as **Exhibit 157**. Notably, Robert Glenn, PhD, former director of NIOSH and consultant to the Talcum Powder industry testified to the same. Deposition of Robert Glenn, October 18, 2018 ("Glenn Dep.") at 341:15-342:12, attached as **Exhibit 158**.

[461] Michael Huncharek, *et al.*, Use of Cosmetic Talc on Contraceptive Diaphragms and Risk of Ovarian Cancer: a Meta-Analysis of Nine Observational Studies, 16 Eur. J. Cancer Prev. 422 (2007), attached as **Exhibit 159**.

[462] *See, e.g.*, Plunkett Rep. at 46 ("When considered together, the scientific literature on the biological effects of talc, as well as asbestos and other constituents routinely found in talc (discussed above), provide sufficient evidence to show that these chemicals produce cellular changes that have been linked to carcinogenesis and that

asbestos *and* fibrous talc, both found in J&J's Talcum Powder Products, are not just carcinogens, but *ovarian* carcinogens.[463] Part of the evidence supporting IARC's assessment was that both minerals caused *inflammation*—the very same mechanism that is described for Talcum Powder Products. Moreover, IARC has found that other contaminants in Talcum Powder Products are also known or probable carcinogens. The presence of any of these contaminants—or all of them -- provide strong evidence that it is *biologically plausible* that J&J's Talcum Powder Products that contain these contaminants are capable of causing ovarian cancer, particularly when considered against the backdrop of the consistent epidemiology showing an association, as discussed above.

J&J now pretends that the presence of asbestos and other carcinogens in its products are not unsupported, unreliable and irrelevant.[464] With respect to the reliability of the evidence, the presence of these carcinogenic constituents—**including asbestos**—are supported by its own internal testing and the published

---

the biological mechanism for carcinogenesis (ovarian and/or lung) following exposure to talcum powder products likely involves induction of a chronic inflammatory response."); Moorman Rep. at 34-35; Siemiatycki Rep. at 64-65.

[463] IARC (2012); IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans, Vol. 42: *Silica and Some Silicates*, (1987), attached as **Exhibit 160**.

[464] *See generally* Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts' Asbestos-Related Opinions.

literature.[465] The PSC's experts reasonably relied the evidence discussed above to support their conclusion regarding biological plausibility. Any weaknesses in their opinions or evidence should be resolved by a jury.

G. THE PSC'S CAUSATION EXPERTS MAY RELIABLY OPINE THAT THE "SPECIFICITY" ASPECT OF THE BRADFORD HILL CAUSATION GUIDELINES ARE SATISFIED WHERE THERE IS EVIDENCE OF SPECIFICITY BETWEEN TALCUM POWDER PRODUCTS AND OVARIAN CANCER GENERALLY AND IN EPITHELIAL OVARIAN CELLS SPECIFICALLY

Another factor to be considered in a Bradford Hill analysis is the "specificity" of the proposed relationship. If a proposed causal association is shown to have a single effect, as opposed to multiple effects, the more likely the proposed causal association.[466] Indeed, where there are multiple carcinogens in Talc, as there are multiple carcinogens in cigarettes, specificity may be even less relevant.[467] For these

---

[465] *See generally* PSC's Memorandum of Law in Response and Opposition to J&J's Motion to Exclude Plaintiffs' Experts' Asbestos-Related Opinions.

[466] *See* Hill (1965) at 297; Rothman, *Modern Epidemiology* at 27-27.

[467] The *Reference Manual* notes the following:

> Cigarette manufacturers have long claimed that because cigarettes have been linked to lung cancer, emphysema, bladder cancer, heart disease, pancreatic cancer, and other conditions, there is no specificity and the relationships are not causal. There is, however, at least one good reason why inferences about the health consequences of tobacco do not require specificity: Because tobacco and cigarette smoke are not in fact single agents but consist of numerous harmful agents, smoking represents exposure to multiple agents, with multiple possible effects. Thus, whereas evidence of specificity may strengthen the case for

reasons, the original criterion of specificity is "widely considered weak or irrelevant from an epidemiologic standpoint."[468]

J&J argues that the association here is highly "unspecific" and that PSC's experts wholly disregarded it.[469] J&J is wrong on both accounts there is evidence of specificity and the PSC's experts address it.[470]

1. There is Evidence that Perineal Talcum Powder Exposure is Specifically Correlated Only to Ovarian Cancer and, more Particularly, to Epithelial Ovarian Cancer

In the broadest sense, there has been no suggestion that there is a causal association between Talcum Powder Products and any other organ or tissue that it comes in contact with, including perineal of anal cancers. Nor has it been suggested that perineal Talcum Powder exposure is associated with other *gynecologic* cancers,

---

causation, lack of specificity does not necessarily undermine it where there is a good biological explanation for its absence." *Ref. Man.* at 606.

[468] K.M. Fedak, *et al., Applying the Bradford Hill criteria in the 21st Century: How Data Integration Has Changed Causal Inference In Molecular Epidemiology*. 12 Emerging Themes in Epidemiology 14 (2015), attached as **Exhibit 161**. For instance, smoking is generally accepted to be a cause of lung cancer, yet smoking is also associated with COPD, heart disease, stroke, and asthma, amongst other diseases. Asbestos, is generally accepted to cause mesothelioma, lung cancer, and ovarian cancer. Asbestos is also generally accepted to cause asbestosis/pulmonary fibrosis, pleural inflammation and thickening.

[469] Defs.' Mem. at 82 and n. 191.

[470] Kane Rep. at 34; McTiernan Rep. at 65; Moorman Rep. at 37; Siemiatycki Rep. at 66; Singh Rep. at 64; Smith-Bindman Rep. at 39; Carson Rep. at 9; Clarke-Pearson Rep. at 8; Smith Rep. at 20; Wolf Rep. at 15.

like cervical or uterine cancer. Indeed, with respect to the "specificity" aspect of Bradford Hill, it has been noted that "*perineal talc exposure is specifically associated with cancer of the ovary and no other organs.*"[471]

There is evidence that the specificity of the Talcum Powder ovarian cancer relationship is even *more* specific than to ovarian cancer generally. The epidemiologic evidence has noted that the association is most closely correlated with cancer of the ovarian *epithelium* (epithelial ovarian cancer) and not to other ovarian cancer like germ cell of stromal cell ovarian cancer. The *epithelial* ovarian cancer data is summarized in *Section III(A)(1)(d), supra*, in relation to the meta-analyses, case control and cohort studies.

Even more specific than that, studies of serous cancer, an epithelial cancer, shows a risk. This includes Gertig (2000), a cohort study (which J&J touts as the highest "level" of observational evidence). That statistically significant data is below:

SEROUS OVARIAN CANCER

Study Type	Year	Author	OR	95%CI
Meta-analysis	2018	Taher	1.38	1.22-1.56
Meta-analysis	2018	Penninkilampi	1.32	1.22-1.43
Meta-analysis	2018	Berge	1.24	1.15-1.34
Case Control	2016	Schildkraut	1.38	1.03-1.85
Case Control	2016	Cramer	1.42	1.19-1.69
Case Control	2009	Wu	1.70	1.27-2.28

[471] Health Canada Assessment at 20 (*citing* Taher, *et al.* (2018)).

Case Control	2008	Merritt	1.21	1.03-1.44
Case Control	2004	Mills	1.77	1.12-2.8
Case Control	1999	Cramer	1.70	1.22-2.39
Case Control	1997	Cook	1.70	1.1-2.50
Cohort	2014	Gertig	1.40	1.02-1.91

This specific association was further noted by Dr. Smith-Bindman in her meta-analysis of the observational data with an OR of 1.52 (95% CI 1.15, 1.88)[472] The observed correlation between Talcum Powder Products and epithelial ovarian cancers is consistent with the plausible mechanism described above which describes Talcum Powder imbedding in the ovarian epithelium.[473]

To suggest that the "proposed association proposed in this litigation is highly unspecific" as J&J does[474] is to ignore the body of science.

[472] Smith-Bindman Report at 34. J&J's attacks on Dr. Smith Bindman's methodology is not unreliable. *See*, discussion *infra*. at Section IV(I).

[473] Plunkett Rep. at 46 (""When considered together, the scientific literature on the biological effects of talc, as well as asbestos and other constituents routinely found in talc (discussed above), provide sufficient evidence to show that these chemicals produce cellular changes that have been linked to carcinogenesis and that the biological mechanism for carcinogenesis (ovarian and/or lung) following exposure to talcum powder products likely involves induction of a chronic inflammatory response."); Moorman Rep. at 34; Kane Rep. at 10-13, 35; McTiernan Rep. at 59-60; Siemiatycki Rep. at 65; Singh Rep. at 58-59; Smith-Bindman Rep. at 15; Wolf Rep. at 15; Carson Rep. at 10; Clarke-Pearson Rep. at 4; Smith Rep. at 17-18; see also Plunkett Dep. at 128:4- 19,189:11-193:25.

[474] Defs.' Mem. at 82.

2. The PSC's Experts Do Not "Ignore" Specificity of Association between Talcum Powder Products and Epithelial Ovarian Cancer

J&J does agree "specificity" is now considered a "less important" Bradford Hill factor than some of the others on the Bradford Hill list.[475] That fact was incorporated into the PSC's experts' analysis. In fact, in describing their "weight of evidence"[476] methodology each of the PSC's experts considered and weighed specificity as against other Bradford Hill Factors and some weighed it less.[477] Contrary to J&J's suggestion, the PSC's experts did not "wholly disregard" specificity.

[475] Defs.' Mem. at 82, n. 191.

[476] *See, e.g.* Tao, et al., *Weight of Evidence: General Principles and Current Applications at Health Canada*, Health Canada (2018), attached as **Exhibit 164**; *In re Mirena Ius Levonorgestrel-Related Products Liab. Litig. (No. II)*, 341 F.Supp.3d 213, 247 (S.D.N.Y. 2018) (Experts should describe how they weighed the evidence).

[477] Kane Rep. at 34; McTiernan Rep. at 65; Moorman Rep. at 37; Siemiatycki Rep. at 66; Singh Rep. at 64; Smith-Bindman Rep. at 39; Carson Rep. at 9; Clarke-Pearson Rep. at 8; Smith Rep. at 20; Wolf Rep. at 15.

H. THE PSC'S CAUSATION EXPERTS MAY RELIABLY OPINE THAT THE OTHER ASPECTS OF THE BRADFORD HILL CAUSATION GUIDELINES ARE ADDRESSED AND/OR SATISFIED

J&J's motion gives short-shrift to the remaining Bradford-Hill aspects, Temporality,[478] Experiment,[479] Coherence[480] and Analogy.[481] Suffice it to say that the PSC's experts considered Temporality,[482] Experiment,[483] Coherence[484] and Analogy[485] in a way that both explains their relevance and how they were weighed against other Bradford Hill Factors. *In re Mirena*, *supra*.

[478] Defs.' Mem. at 84.

[479] Defs.' Mem. at 92.

[480] Defs.' Mem. at 84.

[481] Defs.' Mem. at 88.

[482] Moorman Rep. at 29; Kane Rep. at 34; McTiernan Rep. at 65; Siemiatycki Rep. at 64; Singh Rep. at 64; Smith-Bindman Rep. at 39; Wolf Rep. at 15; Carson Rep. at 9; Clarke-Pearson Rep. at 8; Smith Rep. at 20.

[483] Moorman Rep. at 38; Kane Rep. at 36-37; McTiernan Rep. at 67-68; Singh Rep. at 66; Smith-Bindman Rep. at 41; Wolf Rep. at 16; Carson Rep. at 10; Clarke-Pearson Rep. at 9; Smith Rep. at 21. Dr. Siemiatycki did not specifically address experiment as part of his analysis because he used the causation factors listed in the *Reference Manual* (experiment not included as a factor) as opposed to the traditional Bradford Hill factors. Siemiatycki Rep. at 62; *Ref. Man.* at 597-606.

[484] Moorman Rep. at 37-38; Kane Rep. at 36; McTiernan Rep. at 67; Siemiatycki Rep. at 67; Singh Rep. at 65-66; Smith-Bindman Rep. at 41; Wolf Rep. at 16; Carson Rep. at 10; Clarke-Pearson Rep. at 9; Smith Rep. at 21.

[485] Moorman Rep. at 38; Kane Rep. at 37; McTiernan Rep. at 29-30; Siemiatycki Rep. at 66-67; Singh Rep. at 66; Smith-Bindman Rep. at 41; Wolf Rep. at 16; Carson Rep. at 10-11; Clarke-Pearson Rep. at 9; Smith Rep. at 21.

a. **Temporality**

Temporality (also called "temporal relationship") means that exposure to the agent under investigation must precede development of disease.[486] This has been called the only necessary Bradford-Hill factor.

A nuance is that exposure should also be outside the known latency period for the disease in question.[487] Clearly, the evidence in this case supports this factor. The latency period for the development of epithelial ovarian cancer is generally considered to be between 20 and 30 years.[488] All studies that investigated the association had exposure of Talcum Powder before development of ovarian cancers, though, as noted, the particular weakness of the cohort studies is that exposure to Talcum Powder may not have been long enough (*i.e.*, the **Gonzalez 2016** cohort study which followed patients for only 6.6 years) to account for the *latency* of disease. In any event, the PSC's causation experts considered and weighed this and found that it supports causation.

[486] *Ref. Man.* at 601.

[487] *Id.*

[488] David M. Purdie, *et al., Ovulation and Risk of Epithelial Ovarian Cancer*, 104 Int'l J. Cancer 228, 231 (2003), attached as **Exhibit 163**.

b. **Experiment**

Experiment usually refers to Randomized Clinical Trials (RCT's) but can also be applied to toxicology studies on animals.[489] As all experts agree, RTC's are impossible to conduct to test the hypothesis that Talcum Powder Products can cause ovarian cancer. Plainly, J&J does not dispute and the PSC agrees that it would be highly unethical to conduct RCT to determine of it could cause disease (in this case cancer).[490] Moreover, even if it was ethical to design, it would be impractical to do so since the latency for ovarian cancer is long.[491] As for animal (toxicology) studies, the PSC's experts discussed this data in the context of biological plausibility, and it supports causation.[492]

The PSC's experts considered and weighed this factor.

[489] Rothman, *Modern Epidemiology* at 29.

[490] *See In re Tylenol*, 198 F.Supp.3d at 457 (unethical to perform a clinical trial to test whether acetaminophen can cause acute liver failure at 4 grams).

[491] McTiernan Rep. at 67 (". . . here, randomized controlled trials are neither feasible nor ethical, similar to smoking and lung cancer. This is because ovarian cancer is a rare disease and typically takes decades to develop to be clinically diagnosable. In addition, because the effects of genital talcum powder product use could be harmful, it would be unethical to conduct a trial of this type."); Kane Rep. at 36 ("The challenge of such a study is that it has been shown that talc-associated ovarian cancer takes years or decades before onset of disease.").

[492] *See supra* at Section III(A)(2).

c. **Coherence**

Coherence "implies that a cause-and-effect interpretation for an association does not conflict with what is known of the natural history and biology of the disease."[493] As set forth above, observational studies that are long enough to account for the development of ovarian cancer and the biologic evidence relied on is consistent with the natural course of ovarian cancer.

Moreover, there is evidence that tubal ligation (which would block the migration of Talcum Powder particles through the genital tract) *reduced* epithelial ovarian cancer which are associated with Talcum Powder but not other types of ovarian cancers which appear not to be associated with Talcum Powder. This was noted outside of litigation by Health Canada when addressing the "coherence" Bradford Hill aspect:

> Coherence: Multiple case-control studies reported a lower risk of ovarian cancer in women who underwent pelvic surgery or tubal ligation (which disrupts the pathway and movement of talc from the lower to the upper genital tract) and suppressed ovulation (as cited by Taher et al., 2018: Cramer et al., 1982, 2016; Whittemore et al., 1988; Rosenblatt et al., 1992; Green et al., 1997; Wong et al., 1999; Mills et al., 2004). As noted in Penninkilampi and Eslick (2018), the main reductions in cancer incidence with tubal ligation were for serous and endometrial tumour types but not for mucinous or clear-cell tumours. Thus, tubal ligation is only effective in reducing the incidence of

[493] Rothman, *Modern Epidemiology* at 29.

> the same tumour types noted to be associated with perineal talc use.[494]

In any event, the PSC's experts considered and weighed this factor.

d. **Analogy**

While analogy is usually considered a less important factor, the PSC's experts have addressed it.[495] Among other things, they have analogized this relationship to Asbestos and the development of cancer, though asbestos may also be a biologically plausible mechanism for the development of ovarian cancer since J&J Talcum Powder has contained asbestos.[496]

I. DR. SMITH-BINDMAN'S META-ANALYSIS SATISFIES *DAUBERT* REQUIREMENTS AND HER OPINIONS ARE ADMISSIBLE

Dr. Smith-Bindman was "asked to review the medical and scientific literature regarding the relationship between genital talcum powder product use and ovarian cancer and determine whether the relationship is causal."[497] Her "report reflects [her] review of medical and scientific publications … (overviews and scientific studies), [her] own analysis, and review of documents shared with [her] by lawyers who

---

[494] *Health Canada Assessment* at 21.

[495] *See supra.* n. 481.

[496] *See supra. Section IV(F)(2)(c).*

[497] Smith-Bindman Rep. at 4.

engaged [her] for this task,"[498] and her independent meta-analysis. "The purpose of the systematic review[499] is to take individual papers that may not have enough statistical power to provide by themselves, individual results that are meaningful. And if the methodology is combinable, to pool the sample size to get greater statistical power to come up with a conclusion."[500]

J&J seeks to exclude the opinions of Dr. Rebecca Smith-Bindman, erroneously arguing that her meta-analysis "flunks" *Daubert* for several reasons. However, Dr. Smith-Bindman would have reached the same conclusions even without the meta-analysis she performed. As Dr. Smith-Bindman testified, "my systematic review ended up with the same estimates as essentially all of the other well-done systematic reviews… But yes, it's the same as the other studies, and so my – my conclusion about the causality of talcum powder products and ovarian cancer would be exactly the same, even without mine."[501]As outlined below, J&J's

[498] *Id.* at 8.

[499] J&J argues that there is no such thing as a "systemic meta-analytic review." *See* Defs.' Mem. at 95. However, as Dr. Smith-Bindman noted, "I don't think there is any difference. They're – they're both trying to describe an unbiased, quantitative review of the medical literature." Smith-Bindman Dep. at 52:3-13; 70:22-71:9 (noting just a subtle distinction that systematic review "implies more scientific rigor."); Smith-Bindman Rep. at 6 (noting that her meta-analyses have been "systematic, meta-analytic, quantitative reviews of the published literature.").

[500] Smith-Bindman Dep. at 101:23-102:4.

[501] Smith-Bindman Dep. at 355:10-19.

position is based upon an inappropriate presentation of the record and J&J's motion to exclude the analysis of Dr. Smith-Bindman should be denied.

1. Dr. Smith-Bindman's Analysis was neither *Post-Hoc* nor Conclusion Driven

J&J is incorrect that Dr. Smith-Bindman's meta-analysis was *post-hoc* and conclusion driven.[502] The basis of their argument is that "she analyzed particular subsets of data from cherry-picked studies ***after*** she reviewed the larger body of literature and formulated a thesis."[503] J&J misrepresents the process followed by Dr. Smith-Bindman by arguing that she "had already reviewed the relevant studies and underlying data," while citing to deposition testimony that simply notes that her "systematic review grew out of my reading the literature and realizing that there was a real gap."[504] As clarified in her deposition, "the direction that my review took was partly informed by having read through a number of articles on the topic. So determining sort of where there was a gap, what was the most important area to focus on. So that was sort of the background."[505]

Dr. Smith-Bindman was not familiar enough with the area of talcum powder use and ovarian cancer to "cherry-pick" the information she looked at. "Prior to

[502] Defs.' Memo. at 96.

[503] *Id.* (emphasis in original).

[504] *Compare* Defs.' Mem. at 98 *with* Smith-Bindman Dep. at 52:18-21.

[505] Smith-Bindman Dep. at 146:13-19.

providing [her] opinions on the association between talcum powder products and ovarian cancer, [she] had not reviewed the relevant literature and had not published in this area. As a result, [she] brought an unbiased perspective to [her] review."[506] Her methodology had multiple steps, including:

(1) literature search to broadly identify all relevant literature;[507]

(2) review of the literature abstracts for articles identified to make sure they have primary data;[508]

(3) creating an approach for abstracting data;[509]

(4) abstracting data;[510]

(5) combining the data statistically;[511]and,

(6) performing a meta-analysis.[512]

---

[506] Smith-Bindman Rep. at 8.

[507] *See* Smith-Bindman Dep. at 146:20-21.

[508] *Id.* at 147:24-148:9.

[509] *Id.* at 148:10-15.

[510] *Id.* at 149:4-16.

[511] *Id.* at 15:4-7.

[512] Dr. Smith-Bindman's approach is much more in depth and methodical than experts in the studies referred to by Defendants. *See Snodgrass v. Ford Motor Co.*, 2002 U.S. Dist. LEXIS 13421, at *43 (expert testifying that he made "*arbitrary* division into two subsets… These were not the only way they could be divided, but they *served the purpose.*" (emphasis in original)); *In re Zoloft (Sertraline Hydrochloride Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 462 (E.D. Pa. 2014) (opinions based upon a "self-selected subset of supportive studies, not the totality of the epidemiological evidence); *Amorgianos v. Amtrak*, 303 F.3d 256, 268 (2d Cir. 2002) (excluding evidence where expert "did not find it necessary" to include additional data that was available, despite having stated that a "proper exposure assessment"

Significantly, her decision to focus on "regular use and HGSOC" (high grade serous ovarian cancer) occurred no later than the second step of her methodological process, before she created a plan on how to abstract the data, before data was abstracted, and well before the data was combined statistically. Dr. Smith-Bindman's approach was much different than represented by J&J. She had not reviewed any ***data*** before implementing her review,[513] and her decisions on how to proceed were not based upon a knowledge of the literature and data. Dr. Smith-Bindman conducted the analysis that she had originally planned to do, analysis related to a plan that was put in place ***before*** she started abstracting or analyzing data.

Dr. Smith-Bindman also faithfully and accurately applied her criteria. She provided a detailed summary in her expert report that outlined her rationales and provided explanations for her literature search, selection criteria, exclusion criteria, definitions of "regular use," types of exposures, analysis, etc.[514] Although J&J

---

would have taken them into consideration). Dr. Smith-Bindman's opinions were based upon the totality of the evidence, but further confirmed by the meta-analysis she conducted. To the extent studies and/or data were not included, Dr. Smith-Bindman provided sound reasons as to why. For example, as it related to exclusion of both Cramer 1999 and Rosenblatt, Dr. Smith-Bindman explained her rationale for excluding the studies, but also ran calculations with and without the studies to make sure that exclusion did not cause statistically significant changes in her analysis.

[513] *See* Defs.' Mem. at 98.

[514] *See* Smith-Bindman Rep. at 30-34.

argues that Dr. Smith-Bindman had no explanation for excluding certain studies, her testimony establishes the opposite. For example, she explained that the reason she did not include the Cramer, 1999 study was because there was "overlap" in the data with the Cramer, 2016 study.[515] Although she could not recall why she excluded Rosenblatt from her final analysis, Dr. Smith-Bindman ran and presented data both including and excluding Rosenblatt to confirm that inclusion/exclusion had no impact.[516] To the extent J&J disagrees with her impact assessment, that represents a challenge to Dr. Smith-Bindman's conclusions and the *Daubert* analysis focuses on the methodology underlying an expert's opinion, ***not*** the expert's conclusions.[517] For the foregoing reasons, J&J's arguments related "conclusion driven" analysis fail.[518]

[515] Smith-Bindman Dep. at 176:14-177:19 (explaining that her notes showed that she excluded Cramer 1999 because of data overlap). *See also* Smith-Bindman Rep. at 31 ("When I found duplicate reports on the same patient group, the largest and most detailed publication was included.").

[516] *Id.* at 178:3-17.

[517] *Daubert*, 509 U.S. at 595.

[518] Defendants' argument regarding that Dr. Smith-Bindman failed to do a quality assessment of the case-control studies in her review is incorrect. *See* Defs.' Memo. at 100. Dr. Smith-Bindman's reference to "[w]ithout assessing the quality of the case-control studies" relates only to the manner in which the studies were listed in Table 5 of her report, providing "a way to get an overview of what they report." *See* Smith-Bindman Rep. at 29-30.

2. Dr. Smith-Bindman Selection of "Regular Use" Studies is Defined and Repeatable

Dr. Smith-Bindman's selection of "regular use" studies were neither highly subjective or undefined.[519] Dr. Smith-Bindman had several paragraphs within her report where she explained how regular use was not only defined, but how she applied and implemented the definition to various studies.[520] Dr. Smith-Bindman's decision to define and apply "regular use" was not arbitrary. She explained that she felt "the most important research question to answer in this review is whether regular exposure to talcum powder is associated with ovarian cancer," and "measuring regular use was a more accurate way to evaluate talcum powder as compared to any use."[521] Although J&J accuses Dr. Smith-Bindman of "broadening" her definition so that she could include certain studies, the accusation is based upon a mischaracterization of her work. Dr. Smith-Bindman defined the process she used to include or exclude studies based upon a definition of "regular use," thereby enabling not only herself but others (including Dr. Hall, the biostatistician) to reproduce the results. As with the issue raised by J&J about her work being

[519] *See* Defs.' Mem. at 101.

[520] *Id.* at 30-32.

[521] *Id.* at 31-32. This process does not contradict the opinions of Dr. Siemiatycki who opined that all data are valid and useful. *See* Defs.' Mem. at 102, n. 246. All data is valid and use, but Dr. Smith-Bindman believed that her approach would provide data that was a more accurate assessment of the issue.

conclusion driven, this challenge is to the conclusions reached based upon the application of Dr. Smith-Bindman's well defined and reproducible methodology[522] and should not be the subject of *Daubert.*

3. Dr. Smith-Bindman's Data and Analysis are Both Accurate and Reliable

Finally, J&J's arguments concerning Dr. Smith-Bindman's data and analysis are incorrect. While Dr Smith-Bindman acknowledged that neither her data abstraction nor that of her statistician were "perfect," the purpose of her employment of an additional person to abstract data was because "a single person can never be perfect."[523] As Dr. Smith-Bindman noted, "Dr. Hall was involved both in abstracting the data as a second set of eyes and in doing the statistical summary.[524] Tellingly, Defendants exaggerate Dr. Smith-Bindman's recognition that nothing is perfect to argue that her work contained numerous errors[525] – it did not.

J&J argues that errors existed in confidence intervals cited by Dr. Smith-Bindman because they did not mirror the confidence intervals in various studies. J&J's argument ignores Dr. Smith-Bindman's valid explanations. As noted in her

---

[522] *See* Smith-Bindman Dep. at 357:1-15 (testimony that someone could take her methodology and reproduce the results, especially since the results of her review were the same as the other reviews that had been done).

[523] Smith-Bindman Dep. at 105:5-21.

[524] *Id.* at 101:14-18.

[525] *See* Defs.' Mem. at 104.

deposition, "the numbers are calculated using the standard errors in the confidence intervals and sample size which vary slightly shifts it from the reported numbers. So you were correct when you said the numbers are not exactly the same, and she explained that that's why that's the case." [526] In regard to the inclusion of individuals due to "double-counting," Dr. Smith-Bindman acknowledged that it could theoretically happen, but that is the reason that she works to make sure such data is excluded. Further, the benefits derived from pooling data – that the final summary is less sensitive to any individual result – reduces any such concern.[527] The same holds true for Defendants' attempts to magnify concerns related to "estimations." As Dr. Smith-Bindman made clear, questions proposed by Jane Hall that referred to estimations did not relate to the abstraction of data and, further, the estimations would be based upon calculations applied to data contained and available in the studies. In fact, the calculations arrived at by Dr. Smith-Bindman are the same as seen in other studies.[528]

---

[526] Smith-Bindman Dep. at 255:19-256:13; *see also Id.* at 257:1-12 ("In the documents that I shared, she specified the – the software that she used, the program that she used. In fact, the way of estimating it, it's actually in my report as well. And so yes, its explained there, and it's in all of the documents that I shared with you.").

[527] *Id.* at 344:1-345:3; 356:10-25 ("So the analysis that I have done is complete. . . But the presentation of the results in a paper would require more beautiful graphics, would require explaining our inclusion and exclusion criteria more fully").

[528] *Id.* at 357:11-16.

Finally, Dr. Smith-Bindman did apply the same rigor as if she were preparing a published report. As Dr. Smith-Bindman indicated, the methods she used were the same methods that she has employed and are generally accepted.[529] In regard to Defendants' argument that more detail about methodology would have to be included if she were to publish her results,[530] Dr. Smith-Bindman clarified that the description in the report would need more detail, but the work would not have to be different.[531] Most importantly, as Dr. Smith-Bindman testified, the work she performed, as submitted, can be replicated.

For the foregoing reasons, J&J's arguments related to the exclusion of Dr. Smith-Bindman should be rejected and their motion to exclude her opinions and testimony should be denied.

J. THE PSC'S EXPERTS OPINIONS ARE RELIABLE AND NOT CONTRARY TO SCIENTIFIC CONSENSUS AND DRS. MOORMAN AND SIEMIATYCKI'S CURRENT OPINIONS ARE FULLY CONSISTENT WITH THEIR PRE-LITIGATION PUBLICATIONS

J&J's final argument is that the PSC's causation experts' opinions are unreliable because, in J&J's view, the "consensus" of the Medical Community is that there is

[529] *Id.* at 154:12-119.

[530] *See* Defs.' Mem. at 107.

[531] *See* Smith-Bindman Dep. at 102:23-103:5; 356:16-25 (analysis is done and complete but she would add more beautiful graphics and explain inclusion and exclusion with a little more detail).

insufficient evidence that talcum powder causes ovarian cancer.[532] They further claim that Drs. Moorman and Siemiatycki's opinions are particularly unreliable because they allegedly "contradict" their prior publications on the topic.[533] Neither of these assertions is true and both are easily dismissed.

As an initial matter, J&J would have this Court believe that the scientific community has reached consensus that talcum powder does not cause ovarian cancer. This is simply not true. The most J&J can say, and the most that it *does* say, is that there are some in the scientific community that have believed at different points in time that the evidence between genital talcum powder use and ovarian cancer was "possible," as IARC said in 2006 and "not conclusive" as Dr. Musser from FDA stated in 2014. These hardly "contradict" the opinions of the PSC's experts, other scientists and regulatory bodies outside the litigation context, who have opined that enough evidence has accumulated through 2019 to cause them to conclude that talcum powder is now a *likely* a cause of ovarian cancer. As set forth above, the opinions expressed by Drs. Siemiatycki and Moorman closely align with *current* regulatory authorities like Health Canada who determined in December 2018 that there was evidence of "cause," or the Institute of Medicine which described as recently as 2016 that the genital use of talc results in a 20-30% increased "risk" of

[532] Defs' Mot at 108-120.

[533] *Id.*

ovarian cancer. Consider as well authors like Drs. Narod who published in 2016 that the relationship is "likely to be causal" and that denial of the association was "disingenuous."[534] Indeed, some of the PSC's experts have expressed their views outside litigation including, for example, Dr. McTiernan who testified before the U.S. Congress on the topic in March 2019 or Dr. Siemiatycki who commented to Health Canada after Health Canada issued its causation assessment in February 2019.

Even if it were to be shown that the PSC's experts did contradict the current views of FDA, which is clearly not the case, the opinions of a well-qualified expert would still be admissible so long as they analyzed the totality of the data according to an appropriate methodology. Indeed, the court in *In Re Testosterone,* which concluded that such disagreements with FDA "is left to the trier of fact."[535]

To be clear, neither Dr. Siemiatycki nor Dr. Moorman "contradict" their prior published opinions as J&J contends.[536] As J&J points out, Dr. Siemiatycki was the chair of IARC's 2006 epidemiology committee that classified talc as a "possible" carcinogen based on evidence collected through 2006—13 years ago. Moreover, Langseth, 2008. A paper on which Dr. Siemiatycki was a co-author, discussed *both*

[534] *See, supra* at *Section III(B)(1).*

[535] *Id.* at *13.

[536] Defs' Mot. at 113-118.

the consistent association between talcum powder and ovarian cancer *and* its biologically plausible mechanism:

> - Epidemiological evidence suggests that use of cosmetic talc in the perineal area may be associated with ovarian cancer risk. The IARC has classified this use of talc as possibly carcinogenic to human beings (group 2B); and,
>
> - The mechanism of carcinogenicity may be related to inflammation. This paper focus on the high degree of consistency in the studies accomplished so far, and what should be the focus in future studies.[537]

Clearly, Dr. Siemiatycki's current opinion is in line with his prior published writing in 2006 and 2008, particularly when considered against the backdrop of more than a decade of new science adding to the body of evidence regarding association, biological plausibility, specificity and dose response.

The same is true with Dr. Moorman, the author of the Schildkraut, 2016 study.[538] In that study, Dr. Moorman stated that her review of the data indicated that talc was a "modifiable risk factor" for ovarian cancer and that the association seen in the case control studies (including hers) were not likely to be the result of recall bias— opinions which are absolutely consistent with what she has stated herein. In Schildkraut, 2016, she further stated that:

[537] Langseth (2008) at 360.

[538] Schildkraut (2016).

> The results of the current study showed that genital powder use was associated with ovarian cancer risk in [African American] women and are consistent with localized chronic inflammation in the ovary due to particulates that travel through a direct transvaginal route. The dose–response observed for duration of genital powder use provides further evidence for the relationship between genital powder and overall [Epithelial Ovarian cancer] risk. Our data suggest that the increased risk due to use of genital powder applies to both serous and nonserous histologic subtypes of EOC.[539]

Clearly, Dr. Moorman's opinions are wholly consistent with her peer-reviewed published work

J&J's attempt to mischaracterize the state of science and the growing consensus in the medical community that there is evidence of general causation and by materially misstating the published work of scientists like Drs. Siemiatycki and Moorman, is itself strong *indici*a that J&J's view of the science is suspect and unreliable. In any event, J&J's concerns go to weight and not admissibility.

V. CONCLUSION

For these reasons, J&J's motion to exclude the general causation opinions of the PSC's expert witnesses should be denied.

Respectfully submitted,

/s/ *Michelle A. Parfitt*
Michelle A. Parfitt
ASHCRAFT & GEREL, LLP
1825 K Street, NW, Suite 700
Washington, DC 20006

[539] *Id.* at 1646.

Tel: 202-783-6400
Fax: 202-416-6392
mparfitt@ashcraftlaw.com

/s/ *P. Leigh O'Dell*
P. Leigh O'Dell
BEASLEY, ALLEN, CROW, METHVIN, PORTIS & MILES, P.C.
218 Commerce Street
Montgomery, AL 36104
Tel: 334-269-2343
Fax: 334-954-7555
Leigh.odell@beasleyallen.com

Plaintiffs' Co-Lead Counsel

/s/ *Christopher M. Placitella*
Christopher M. Placitella
COHEN, PLACITELLA & ROTH, P.C.
127 Maple Avenue
Red Bank, NJ 07701
Tel: 732-747-9003
Fax: 732-747-9004
cplacitella@cprlaw.com

Plaintiffs' Liaison Counsel

PLAINTIFFS' EXECUTIVE COMMITTEE:

Warren T. Burns
BURNS CHAREST LLP
500 North Akard Street, Suite 2810
Dallas, TX 75201
Tel: 469-904-4551
Fax: 469-444-5002
wburns@burnscharest.com

Richard Golomb
GOLOMB & HONIK, P.C.
1515 Market Street, Suite 1100
Philadelphia, PA 19102
Tel: 215-985-9177
rgolomb@golombhonik.com

Richard H. Meadow
THE LANIER LAW FIRM PC
6810 FM 1960 West
Houston, TX 77069

Hunter J. Shkolnik
NAPOLI SHKOLNIK PLLC
360 Lexington Avenue, 11thFloor
New York, NY 10017

Tel: 713-659-5200
Fax: 713-659-2204
richard.meadow@lanierlawfirm.com

Tel: 212-397-1000
hunter@napolilaw.com

PLAINTIFFS' STEERING COMMITTEE:

Laurence S. Berman
Michael M. Weinkowitz
LEVIN, SEDRAN & BERMAN LLP
510 Walnut Street, Suite 500
Philadelphia, PA 19106
Tel: 215-592-1500
Fax: 215-592-4663
lberman@lfsblaw.com

Timothy G. Blood
BLOOD, HURST & O'REARDON, LLP
701 B Street, Suite 1700
San Diego, CA 92101
Tel: 619-338-1100
Fax: 619-338-1101
tblood@bholaw.com

Sindhu S. Daniel
BARON & BUDD, P.C.
3102 Oak Lawn Avenue, #1100
Dallas, TX 75219
Tel: 214-521-3605
Fax: 214-520-1181
sdaniel@baronbudd.com

Jeff S. Gibson
WAGNER REESE, LLP
11939 N. Meridian St.
Carmel, IN 46032
Tel: (317) 569-0000
Fax: (317) 569-8088
jgibson@wagnerreese.com

Kristie M. Hightower
LUNDY, LUNDY, SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Tel: 337-439-0707
Fax: 337-439-1029
khightower@lundylawllp.com

Daniel R. Lapinski
MOTLEY RICE LLC
210 Lake Drive East, Suite 101
Cherry Hill, NJ 08002
Tel: 856-667-0500
Fax: 856-667-5133
dlapinski@motleyrice.com

Victoria Maniatis
SANDERS PHILLIPS GROSSMAN, LLC
100 Garden City Plaza, Suite 500
Garden City, NJ 11530
Tel: 516-640-3913
Fax: 516-741-0128
vmaniatis@thesandersfirm.com

Carmen S. Scott
MOTLEY RICE LLC
28 Bridgeside Boulevard
Mount Pleasant, SC 29464
Tel: 843-216-9162
Fax: 843-216-9450
cscott@motleyrice.com

Eric H. Weinberg
THE WEINBERG LAW FIRM
149 Livingston Avenue
New Brunswick, NJ 08901
Tel: 732-246-7080
Fax: 732-246-1981
ehw@erichweinberg.com

Christopher V. Tisi
LEVIN PAPANTONIO
316 South Baylen St.
Pensacola, FL 32502
(850) 435-7000
ctisi@levinlaw.com

Richard L. Root
MORRIS BART, LLC
Pan America Life Center
601 Poydras St., 24th Fl.
New Orleans, LA 70130
Tel. 504-525-8000
Fax: 504-599-3392
rroot@morrisbart.com